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(21) International Application Number: PCT/JP00/00017 (22) International Filing Date: 6 January 2000 (06.01.00) (30) Priority Data: PP 8180 14 January 1999 (14.01.99) AU (71) Applicant (for all designated States except US): FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). (72) Inventors; and (75) Inventors/Applicants (for US only): YAMADA, Akira [JP/JP]; 4-8-30, Sawada, Fujiidera-shi, Osaka 583-0011 (JP). AOKI, Satoshi [JP/JP]; 2-38-3, Maborikaigan, Yokosuka-shi, Kanagawa 239-0801 (JP). (74) Agent: TABUSHI, Eiji; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532-8514 (JP).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: AMIDE COMPOUNDS <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> $\begin{array}{c} R^1-A-N-E \\ \quad \\ R^3 \quad R^4 \end{array} \quad X-Y-Q-R^2 \quad (1)$ </div> <div style="text-align: center;"> $\begin{array}{c} O \\ \\ -C- \end{array} \quad (1)$ </div> </div>			
(57) Abstract <p>This invention relates to new amide compounds having the potentiation of the cholinergic activity, etc., and represented by general formula (1), wherein R¹ is acyl, R² is lower alkyl, etc., A is a single bond, (1) or -SO₂-, E is lower alkylene, etc., X is CH or N, Y is a single bond, etc., Q is -CH₂-, etc., and R³ and R⁴ are taken together to form lower alkylene, etc., and pharmaceutically acceptable salts thereof, to processes for preparation thereof and a pharmaceutical composition comprising the same.</p>			

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DESCRIPTION

AMIDE COMPOUNDS

5 TECHNICAL FIELD

This invention relates to new amide compounds and pharmaceutically acceptable salts thereof which are useful as a medicament.

10 BACKGROUND ART

Some aminopiperazine derivatives have been known as useful anti-amnesia or anti-dementia agents, for example, in PCT International Publication Nos. WO 91/01979 and WO 98/35951.

15

DISCLOSURE OF INVENTION

This invention relates to new amide compounds and pharmaceutically acceptable salts thereof.

More particularly, it relates to new amide compounds and
20 pharmaceutically acceptable salts thereof which have the
potentiation of the cholinergic activity, to processes for
the preparation thereof, to a pharmaceutical composition
comprising the same, and to a method for the treatment and/or
prevention of disorders in the central nervous system for
25 mammals, and more particularly to method for the treatment
and/or prevention of amnesia, dementia (e.g., senile dementia,
Alzheimer's dementia, dementia associated with various
diseases such as cerebral vascular dementia, cerebral post-
traumatic dementia, dementia due to brain tumor, dementia due
30 to chronic subdural hematoma, dementia due to normal pressure
hydrocephalus, post-meningitis dementia, Parkinson's disease
type dementia, etc.), and the like. Additionally, the object
compound is expected to be useful as therapeutical and/or
preventive agents for schizophrenia, depression, stroke, head
35 injury, nicotine withdrawal, spinal cord injury, anxiety,

pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism.

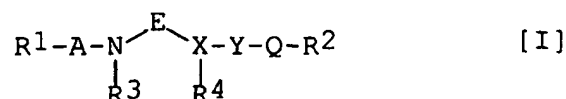
One object of this invention is to provide new and
5 useful amide compounds and pharmaceutically acceptable salts thereof which possess the potentiation of the cholinergic activity.

Another object of this invention is to provide processes for preparation of said amide compounds and salts thereof.

10 A further object of this invention is to provide a pharmaceutical composition comprising, as an active ingredient, said amide compounds and pharmaceutically acceptable salt thereof.

Still further object of this invention is to provide a
15 therapeutic method for the treatment and/or prevention of aforesaid diseases in mammals, using said amide compounds and pharmaceutically acceptable salts thereof.

The amide compounds of this invention are new and can be
20 represented by the following general formula [I]:



25

wherein R¹ is acyl,

R² is lower alkyl, lower alkoxy, lower alkylamino, lower alkenyl, lower alkenyloxy, lower alkenylamino, lower alkynyl, lower alkynyloxy, lower alkynylamino,
30 cyclo(lower)alkyl, cyclo(lower)alkyloxy, cyclo(lower)alkylamino, aryl, aryloxy, arylamino, a heterocyclic group or amino substituted with a heterocyclic group, each of which may be substituted with suitable substituent(s); or acyl;

35

A is a single bond, $\overset{\text{O}}{\parallel}\text{C}-$ or $-\text{SO}_2-$,

E is lower alkylene optionally substituted with suitable substituent(s),

5 X is CH or N,

Y is a single bond, lower alkylene or $\overset{\text{R}^5}{\underset{|}{\text{N}}}-$
(wherein R^5 is hydrogen, lower alkyl,
substituted-lower alkyl, an N-protective group,
aryl, acyl or a heterocyclic group),

10 Q is $-\text{CH}_2-$, $\overset{\text{O}}{\parallel}\text{C}-$, $-\text{SO}_2-$ or $-\text{N}=\text{CH}-$, and

R^3 and R^4 are each hydrogen or lower alkyl, or are
taken together to form lower alkylene optionally
condensed with a cyclic hydrocarbon or a
15 heterocyclic ring,

provided that when X is N,

then 1) Y is a single bond, and

Q is $-\text{CH}_2-$, $\overset{\text{O}}{\parallel}\text{C}-$ or $-\text{SO}_2-$, or

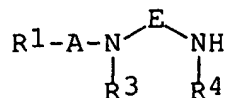
20 2) Y is lower alkylene,

and pharmaceutically acceptable salts thereof.

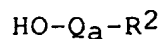
The object compound [I] or its salt can be prepared by
processes as illustrated in the following reaction schemes.

25

Process 1



+



30

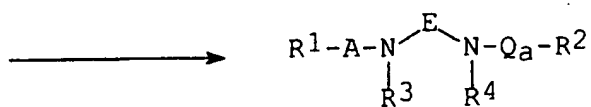
[II]

or its salt

[III]

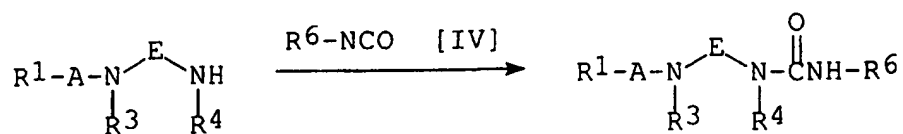
or its reactive derivative
at the carboxy or sulfo
group, or a salt thereof

35



[Ia]

or its salt

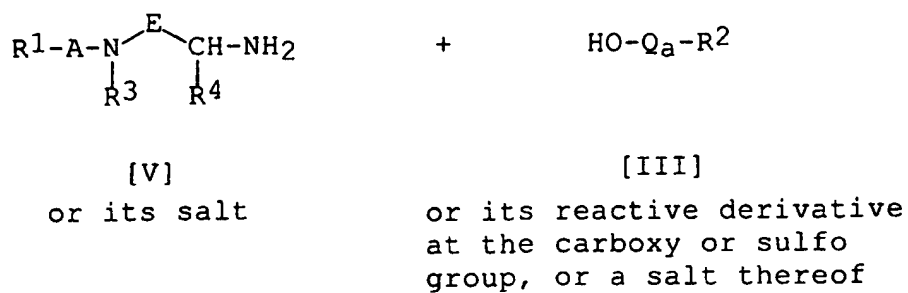
Process 2

[II]

or its salt

[Ib]

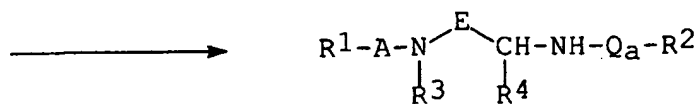
or its salt

Process 3

[V]

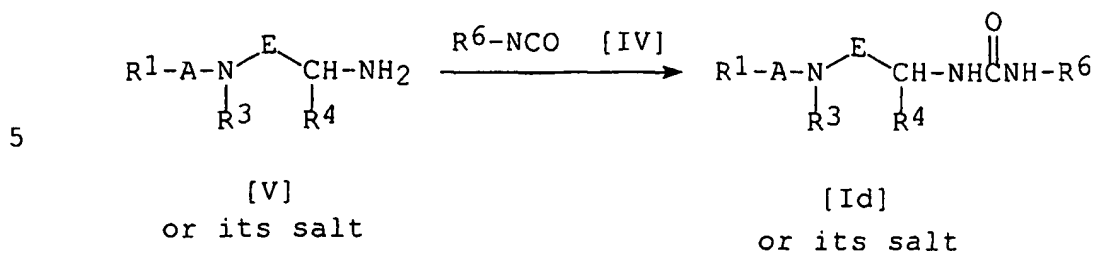
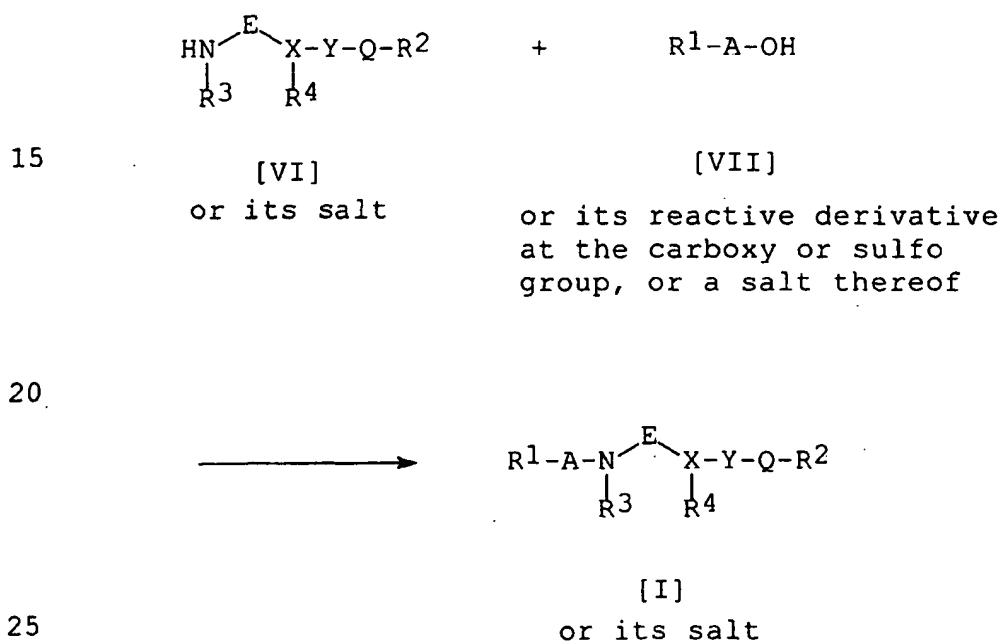
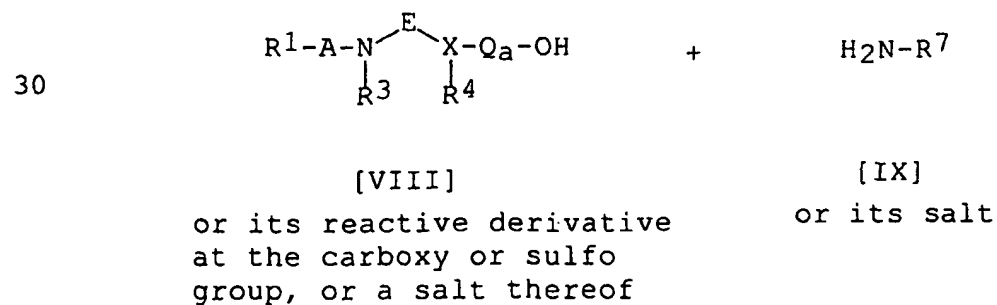
or its salt

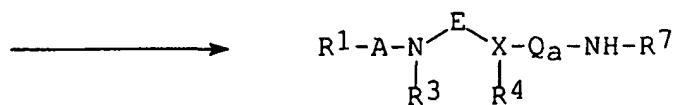
[III]

or its reactive derivative
at the carboxy or sulfo
group, or a salt thereof

[Ic]

or its salt

Process 410 Process 5Process 6

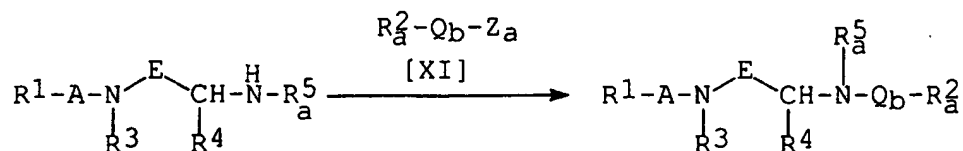


5

[Ie]
or its salt

Process 7

10



[X]

or its salt

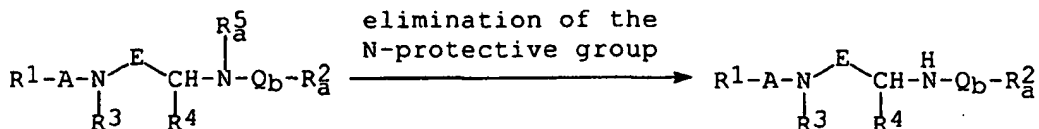
[If]

or its salt

15

Process 8

20



[If]

or its salt

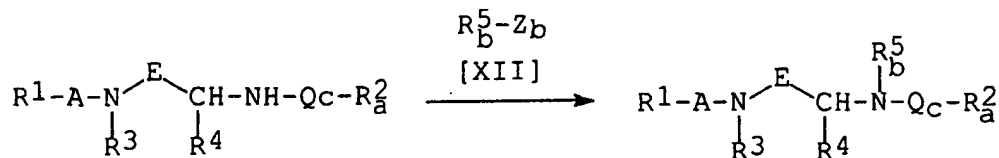
[Ig]

or its salt

25

Process 9

30



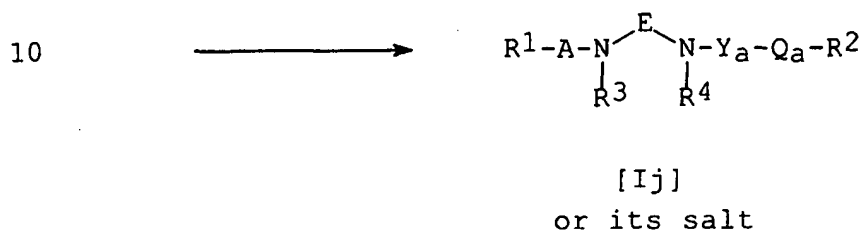
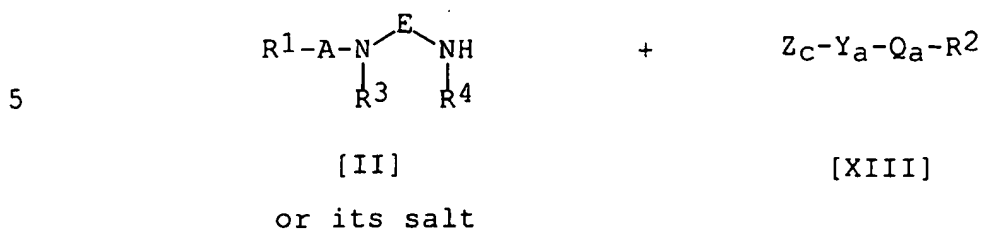
[Ih]

or its salt

[Ii]

or its salt

35

Process 10

15

wherein R^1 , R^2 , R^3 , R^4 , A, E, Q, X and Y are each as defined above,

20

Q_a is $\text{-}\overset{\text{O}}{\parallel}\text{C-}$ or $\text{-SO}_2\text{-}$,

R^6 is aryl which may be substituted with suitable substituent(s), or pyridyl,

R^7 is lower alkyl, lower alkenyl, lower alkynyl, cyclo(lower)alkyl, aryl or a heterocyclic group, each of which may be substituted with suitable substituent(s),

25

R_a^5 is an N-protective group,

R_a^2 is lower alkyl, lower alkenyl, lower alkynyl, cyclo(lower)alkyl, aryl or a heterocyclic group, each of which may be substituted with suitable substituent(s),

30

Q_b is $\text{-CH}_2\text{-}$, $\text{-}\overset{\text{O}}{\parallel}\text{C-}$, or $\text{-SO}_2\text{-}$,

Z_a is an acid residue,

35

Q_c is $\text{-}\overset{\text{O}}{\parallel}\text{C-}$,

R_D^5 is lower alkyl,
 Z_b is an acid residue,
 Z_c is an acid residue, and
 Y_a is lower alkylene.

5

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

10

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

The lower moiety in the term "lower alkenyl", "lower alkenyloxy", "lower alkenylamino", "lower alkynyl", "lower alkynyloxy" and "lower alkynylamino" is intended to mean a group having 2 to 6 carbon atoms.

The lower moiety in the terms "cyclo(lower)alkyl", "cyclo(lower)alkyloxy" and "cyclo(lower)alkylamino" is intended to mean a group having 3 to 6 carbon atoms.

Suitable "lower alkyl" and lower alkyl moiety in the terms "substituted-lower alkyl", "ar(lower)alkyl", "halo(lower)alkyl", "lower alkylamino", "lower alkylsilyl", "lower alkylthio" and "lower alkylsulfonyl" may be a straight or branched C_1 - C_6 alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, ethylpropyl, hexyl or the like, in which preferable one is methyl.

Suitable "lower alkenyl" and lower alkenyl moiety in the terms "lower alkenyloxy" and "lower alkenylamino" may be a straight or branched C_2 - C_6 alkenyl such as ethenyl, propenyl, butenyl, pentenyl, hexenyl, isopropenyl, butadienyl, pentadienyl, hexadienyl or the like, in which preferable one is ethenyl, propenyl or butadienyl.

Suitable "lower alkynyl" and lower alkynyl moiety in the terms "lower alkynyloxy" and "lower alkynylamino" may be a straight or branched C_2 - C_6 alkynyl such as ethynyl, propargyl,

butynyl or the like, in which preferable one is ethynyl.

Suitable "cyclo(lower)alkyl" and cyclo(lower)alkyl moiety in the terms "cyclo(lower)alkyloxy" and "cyclo(lower)alkylamino" may be cyclo(C₃-C₆)alkyl such as
5 cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, in which preferable one is cyclopropyl.

Suitable "aryl" and aryl or ar moiety in the terms "ar(lower)alkoxy", "aryloxy", "arylamino", "arylsulfonyl", "aroxy" and "ar(lower)alkyl" may be phenyl, naphthyl, phenyl
10 substituted with lower alkyl [e.g. tolyl, xylyl, mesityl, cumenyl, di(tert-butyl)phenyl, etc.] and the like, in which preferable one is phenyl or tolyl.

Suitable "ar(lower)alkyl" may be benzyl, phenethyl, phenylpropyl, benzhydryl, trityl and the like, in which
15 preferable one is benzyl.

Suitable "lower alkylene" and lower alkylene moiety in the term "lower alkylenedioxy" may be a straight or branched C₁-C₆ alkylene such as methylene, ethylene, trimethylene, propylene, tetramethylene, pentamethylene, hexamethylene,
20 ethylethylene or the like, in which preferable one is methylene, ethylene or trimethylene.

Suitable "lower alkoxy" and lower alkoxy moiety in the terms "ar(lower)alkoxy" and "halo(lower)alkoxy" may be a straight or branched C₁-C₆ alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, methylpropoxy, butoxy, isobutoxy, tert-
25 butoxy, pentyloxy, hexyloxy or the like, in which preferable one is methoxy or tert-butoxy.

Suitable "ar(lower)alkoxy" may be benzyloxy, phenethyloxy, phenylpropoxy, benzhydryloxy, trityloxy and the
30 like.

Suitable "halogen" and halo moiety in the term "halo(lower)alkyl" may be fluorine, chlorine, bromine and iodine, in which preferable one is fluorine, chlorine or iodine.

35 Suitable "halo(lower)alkyl" may be lower alkyl

substituted with one or more halogens such as chloromethyl, dichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, pentachloroethyl or the like, in which preferable one is trifluoromethyl.

5 Suitable "halo(lower)alkoxy" may be lower alkoxy substituted with one or more halogens such as chloromethoxy, dichloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, pentachloromethoxy or the like, in which preferable one is trifluoromethoxy.

10 Suitable "lower alkylamino" may be mono or di(lower alkylamino) such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, tert-butylamino, isobutylamino, pentylamino, hexylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, diisopropylamino, dipentylamino,
15 dihexylamino, N-methylethylamino or the like, in which preferable one is dimethylamino.

 Suitable "lower alkylsilyl" may be mono, di, or tri(lower)alkylsilyl such as trimethylsilyl, dimethylsilyl, triethylsilyl or the like, in which preferable one is
20 trimethylsilyl.

 Suitable "lower alkylenedioxy" may be methylenedioxy, ethylenedioxy and the like, in which preferable one is methylenedioxy.

 Suitable "heterocyclic group" may be one containing at
25 least one hetero atom selected from nitrogen, sulfur and oxygen atom, and may include saturated or unsaturated, monocyclic or polycyclic heterocyclic group, and preferable heterocyclic group may be N-containing heterocyclic group such as unsaturated 3 to 6-membered heteromonocyclic group
30 containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl [e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.], tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.;
35 saturated 3 to 7-membered heteromonocyclic group containing 1

- to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, homopiperazinyl, etc.];
unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl,
5 benzimidazolyl, quinolyl, isoquinolyl, imidazopyridyl, indazolyl, benzotriazolyl, tetrazolo-pyridazinyl [e.g. tetrazolo[1,5-b]pyridazinyl, etc.], quioxalinyl, etc.;
- unsaturated 3 to 6-membered heteromonocyclic group containing
10 an oxygen atom, for example, pyranyl, furyl, etc.;
- saturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, 1H-tetrahydropyranyl, tetrahydrofuranlyl, etc.;
- unsaturated 3 to 6-membered heteromonocyclic group containing
15 1 to 2 sulfur atoms, for example, thienyl, etc.;
- unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.], oxazolinyl [e.g.
20 2-oxazolinyl, etc.], etc.;
- saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl, etc.];
- unsaturated condensed heterocyclic group containing 1 to 2
25 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzofurazanyl, benzoxazolyl, benzoxadiazolyl, etc.];
- unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g. 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.], etc.;
- 30 saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g. thiazolidinyl, etc.];
- unsaturated condensed heterocyclic group containing 1 to 2
35 sulfur atoms and 1 to 3 nitrogen atoms [e.g. benzothiazolyl,

benzothiadiazolyl, etc.];

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms [e.g. benzofuranyl, benzodioxolyl, chromanyl, etc.] and the like.

5 Said "heterocyclic group" may be substituted with lower alkyl as exemplified above, in which preferable one is thienyl, pyridyl, methylpyridyl, quinolyl, indolyl, quinoxaliny, benzofuranyl or tetramethylchromanyl, and more preferable one is pyridyl.

10 Suitable "acyl" may be carboxy; esterified carboxy; carbamoyl substituted with lower alkyl, aryl, ar(lower)alkyl, arylsulfonyl, lower alkylsulfonyl or a heterocyclic group; substituted or unsubstituted arylsulfonyl; lower alkylsulfonyl; cyclo(lower)alkylcarbonyl;
15 lower alkanoyl; substituted or unsubstituted aroyl; a heterocycliccarbonyl and the like.

The esterified carboxy may be substituted or unsubstituted lower alkoxycarbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl,
20 tert-butoxycarbonyl, hexyloxycarbonyl, 2-iodoethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, etc.], substituted or unsubstituted aryloxycarbonyl [e.g. phenoxycarbonyl, 4-nitrophenoxycarbonyl, 2-naphthyloxycarbonyl, etc.], substituted or unsubstituted ar(lower)alkoxycarbonyl [e.g.
25 benzyloxycarbonyl, phenethyloxycarbonyl, benzhydryloxycarbonyl, 4-nitrobenzyloxycarbonyl, etc.] and the like, in which preferable one is unsubstituted lower alkoxycarbonyl and more preferable one is methoxycarbonyl or tert-butoxycarbonyl.

30 The carbamoyl substituted with lower alkyl may be methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, N-methyl-N-ethylcarbamoyl and the like.

The carbamoyl substituted with aryl may be
35 phenylcarbamoyl, naphthylcarbamoyl, lower alkyl-substituted

phenylcarbamoyl [e.g. tolylcarbamoyl, xylylcarbamoyl, etc.] and the like.

The carbamoyl substituted with ar(lower)alkyl may be benzylcarbamoyl, phenethylcarbamoyl, phenylpropylcarbamoyl
5 and the like, in which preferable one is benzylcarbamoyl.

The carbamoyl substituted with arylsulfonyl may be phenylsulfonylcarbamoyl, tolylsulfonylcarbamoyl and the like.

The carbamoyl substituted with lower alkylsulfonyl may be methylsulfonylcarbamoyl, ethylsulfonylcarbamoyl and the
10 like.

The carbamoyl substituted with a heterocyclic group may be one substituted with a heterocyclic group as mentioned above.

15 The lower alkanoyl may be formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl and the like, in which preferable one is acetyl or pivaloyl.

The substituted or unsubstituted aroyl may be benzoyl, naphthoyl, toluoyl, di(tert-butyl)benzoyl,
20 halo(lower)alkoxybenzoyl [e.g. trifluoromethoxybenzoyl, etc.] and the like, in which preferable one is benzoyl or trifluoromethoxybenzoyl.

The substituted or unsubstituted arylsulfonyl may be phenylsulfonyl, tolylsulfonyl, halophenylsulfonyl [e.g.
25 fluorophenylsulfonyl, etc.] and the like, in which preferable one is fluorophenylsulfonyl.

The lower alkylsulfonyl may be methylsulfonyl, ethylsulfonyl and the like, in which preferable one is methylsulfonyl.

30 The cyclo(lower)alkylcarbonyl may be cyclo(C₃-C₆)-alkylcarbonyl such as cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl or cyclohexylcarbonyl, in which preferable one is cyclopropylcarbonyl.

The heterocyclic moiety in the term
35 "a heterocycliccarbonyl" may be one mentioned above as a

heterocyclic group.

Suitable "acid residue" may be halogen [e.g. fluoro, chloro, bromo, iodo], arenesulfonyloxy [e.g. benzenesulfonyloxy, tosyloxy, etc.], alkanesulfonyloxy [e.g. mesyloxy, ethanesulfonyloxy, etc.], and the like, in which preferable one is halogen.

Suitable "N-protective group" may be common N-protective group such as substituted or unsubstituted lower alkanoyl [e.g. formyl, acetyl, propionyl, trifluoroacetyl, etc.], lower alkoxy carbonyl [e.g. tert-butoxycarbonyl, tert-amylloxycarbonyl, etc.], substituted or unsubstituted aralkyloxycarbonyl [e.g. benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, etc.], 9-fluorenylmethoxycarbonyl, substituted or unsubstituted arenesulfonyl [e.g. benzenesulfonyl, tosyl, etc.], nitrophenylsulfenyl, aralkyl [e.g. trityl, benzyl, etc.] or the like, in which preferable one is lower alkoxy carbonyl and more preferable one is tert-butoxycarbonyl.

Suitable "cyclic hydrocarbon" may be a saturated or unsaturated cyclic hydrocarbon such as cyclopentane, cyclohexane, benzene, naphthalene, indan, indene or the like.

Suitable "substituted-lower alkyl" may be lower alkyl substituted with halogen, aryl, acyl, lower alkoxy, aryloxy and the like, in which preferable one is benzyl.

Suitable "heterocyclic ring" may be one which is a heterocyclic group, as mentioned above, added by hydrogen.

Preferred "acyl" for R^1 may be lower alkanoyl; lower alkoxy carbonyl; aroyl optionally substituted with halo(lower)alkoxy; arylsulfonyl optionally substituted with halogen; lower alkylsulfonyl; or cyclo(lower)alkylcarbonyl, in which more preferable one is acetyl, pivaloyl, methoxycarbonyl, tert-butoxycarbonyl, benzoyl, trifluoromethoxybenzoyl, fluorophenylsulfonyl, methylsulfonyl

or cyclopropylcarbonyl.

Preferred "suitable substituent" as the substituent of lower alkyl, lower alkoxy, lower alkylamino, lower alkenyl, lower alkenyloxy, lower alkenylamino, lower alkynyl, lower alkynyloxy, lower alkynylamino, cyclo(lower)alkyl, cyclo(lower)alkyloxy, cyclo(lower)alkylamine, aryl, aryloxy, arylamino, a heterocyclic group or amino substituted a heterocyclic group for R^2 may be halo(lower)alkyl, halo(lower)alkoxy, lower alkenyl, lower alkynyl, lower alkylamino, acylamino, acyl, lower alkylsilyl, lower alkoxy, aryl, lower alkylenedioxy, acyloxy, hydroxy, nitro, amino, cyano, halogen, aryloxy, lower alkylthio and the like.

Preferred "aryl which may be substituted with suitable substituent(s)" for R^2 may be aryl optionally substituted with halogen, in which more preferable one is fluorophenyl.

Preferred "aryl amino which may be substituted with suitable substituent(s)" for R^2 may be aryl amino optionally substituted with halogen, in which preferable one is phenyl amino or fluorophenyl amino.

Preferred "aryloxy which may be substituted with suitable substituent(s)" for R^2 may be aryloxy optionally substituted with halogen, in which preferable one is fluorophenoxy.

Preferred "lower alkylene" for Y may be methylene.

Preferred "lower alkyl" for R^5 in Y may be methyl.

Preferred "N-protective group" for R^5 in Y may be tert-butoxycarbonyl.

Preferred "suitable substituent" as the substituent of lower alkylene for E may be oxo, lower alkyl, hydroxy(lower)alkyl or acyl, in which more preferable one is oxo, dioxo, methyl, dimethyl, hydroxymethyl, or benzylcarbamoyle.

Preferred "lower alkylene" for E may be methylene, ethylene or trimethylene, and more preferable one is ethylene.

Preferred "lower alkyl" for R^3 and R^4 may be methyl.

Preferred "lower alkylene which R^3 and R^4 are taken together to form" may be ethylene or trimethylene.

Preferred "a cyclic hydrocarbon with which lower alkylene is condensed" may be benzene.

- 5 Preferred compound [I] is one having lower alkanoyl, lower alkoxy carbonyl, aroyl, aroyl substituted with halo(lower)alkoxy, lower alkylsulfonyl, arylsulfonyl, arylsulfonyl substituted with halogen or cyclo(lower)alkylcarbonyl for R^1 , aryl, aryloxy or arylamino, each aryl of which may be substituted with halogen; pyridyl; 10 or pyridylamino for R^2 , a single bond for

- A, ethylene for E, CH for X, $\begin{array}{c} \text{H} \\ | \\ -\text{N}- \end{array}$ for Y, $\begin{array}{c} \text{O} \\ || \\ -\text{C}- \end{array}$ for Q, and ethylene for R^3 and R^4 to be taken together to form, or 15 lower alkanoyl, lower alkoxy carbonyl, aroyl, aroyl substituted with halo(lower)alkoxy, lower alkylsulfonyl, arylsulfonyl, arylsulfonyl substituted with halogen or cyclo(lower)alkylcarbonyl for R^1 , aryl, aryloxy or arylamino, each aryl of which may be substituted with halogen; pyridyl; 20 or pyridylamino for R^2 , a single bond for

A, ethylene for E, N for X, a single bond for Y, $\begin{array}{c} \text{O} \\ || \\ -\text{C}- \end{array}$ for Q, and ethylene for R^3 and R^4 to be taken together to form.

- Suitable pharmaceutically acceptable salts of the object 25 compound [I] are conventional non-toxic salts and include acid addition salt such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, 30 benzenesulfonate, toluenesulfonate, etc.], a salt with an amino acid [e.g. aspartic acid salt, glutamic acid salt, etc.], a metal salt such as an alkali metal salt [e.g. sodium salt, potassium salt, etc.] and alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.] and the like.

The processes for preparing the object compound [I] are explained in detail in the following.

Process 1

5 The compound [Ia] or its salt can be prepared by reacting a compound [II] or its salt with a compound [III] or its reactive derivative at the carboxy or sulfo group, or a salt thereof.

10 Suitable salts of the compounds [Ia] and [II] may be the same as those exemplified for the compound [I].

 Suitable salts of the compound [III] and its reactive derivative at the carboxy or sulfo group may be metal salt or alkaline earth metal salt as exemplified for the compound [I].

15 Suitable reactive derivative at the carboxy or sulfo group or the compound [III] may include an ester, an acid halide, an acid anhydride and the like. The suitable examples of the reactive derivatives may be an acid halide [e.g. acid chloride, acid bromide, etc.];
a symmetrical acid anhydride; a mixed acid anhydride with an
20 acid such as aliphatic carboxylic acid [e.g. acetic acid, pivalic acid, etc.], substituted phosphoric acid [e.g. dialkylphosphoric acid, diphenylphosphoric acid, etc.];
an ester such as substituted or unsubstituted lower alkyl ester [e.g. methyl ester, ethyl ester, propyl ester, hexyl
25 ester, trichloromethyl ester, etc.], substituted or unsubstituted ar(lower)alkyl ester [e.g. benzyl ester, benzhydryl ester, p-chlorobenzyl ester, etc.], substituted or unsubstituted aryl ester [e.g. phenyl ester, tolyl ester, 4-nitrophenyl ester, 2,4-dinitrophenyl ester,
30 pentachlorophenyl ester, naphthyl ester, etc.], or an ester with N,N-dimethylhydroxylamine, N-hydroxysuccinimide, N-hydroxyphthalimide or 1-hydroxybenzotriazole, 1-hydroxy-6-chloro-1H-benzotriazole, or the like. These reactive derivatives can be optionally selected according to the kind
35 of the compound [III] to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, chloroform, methylene chloride, ethylene dichloride, tetrahydrofuran, acetonitrile, ethyl acetate, N,N-dimethylformamide, pyridine
5 or any other organic solvent which does not adversely influence the reaction. Among these solvents, hydrophilic solvent may be used in a mixture with water.

The reaction is also preferably carried out in the presence of a conventional base such as triethylamine,
10 diisopropylethylamine, pyridine, N,N-dimethylaminopyridine, etc., or a mixture thereof.

When the compound [III] is used in a free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing
15 agent such as N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, thionyl chloride, oxalyl chloride, lower alkoxycarbonyl halide [e.g. ethyl chloroformate, isobutyl chloroformate, etc.],
20 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole, or the like.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

25 Process 2

The compound [Ib] or its salt can be prepared by reacting a compound [II] or its salt with a compound [IV].

Suitable salts of the compounds [Ib] and [II] may be the same as those exemplified for the compound [I].

30 This reaction is usually carried out in a solvent such as dioxane, tetrahydrofuran, benzene, toluene, chloroform, methylene chloride or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the
35 reaction is usually carried out under cooling to warming.

Process 3

The compound [Ic] or its salt can be prepared by reacting a compound [V] or its salt with a compound [III] or its reactive derivative at the carboxy or sulfo group, or a salt thereof.

Suitable salts of the compounds [Ic] and [V] may be the same as those exemplified for the compound [I].

Suitable salts of the compound [III] and its reactive derivative at the carboxy or sulfo group may be metal salt or alkaline earth metal salt as exemplified for the compound [I].

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction condition [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

Process 4

The compound [Id] or its salt can be prepared by reacting a compound [V] or its salt with a compound [IV].

Suitable salts of the compounds [Id] and [V] may be the same as those exemplified for the compound [I].

This reaction can be carried out in substantially the same manner as Process 2, and therefore the reaction mode and reaction condition [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those explained in Process 2.

Process 5

The compound [I] or its salt can be prepared by reacting a compound [VI] or its salt with a compound [VII] or its reactive derivative at the carboxy or sulfo group, or a salt thereof.

Suitable salt of the compound [VI] may be acid addition salt as exemplified for the compound [I].

Suitable salts of the compound [VII] and its reactive derivative at the carboxy or sulfo group may be metal salt or alkaline earth metal salt as exemplified for the compound [I].

This reaction can be carried out in substantially the
5 same manner as Process 1, and therefore the reaction mode and reaction condition [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

10 Process 6

The compound [Ie] or its salt can be prepared by reacting a compound [VIII] or its reactive derivative at the carboxy group or sulfo group, or a salt thereof with a compound [IX] or its salt.

15 Suitable salts of the compounds [Ie], [VIII] and its reactive derivative at the carboxy or sulfo group may be the same as those exemplified for the compound [I].

Suitable salt of the compound [IX] may be acid addition salt as exemplified for the compound [I].

20 This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction condition [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

25

Process 7

The compound [If] can be prepared by reacting a compound [X] or its salt with a compound [XI].

Suitable salts of the compounds [If] and [X] may be the
30 same as those exemplified for the compound [I].

The present reaction is preferably carried out in the presence of base such as an alkali metal [e.g. lithium, sodium, potassium, etc.], alkaline earth metal [e.g. calcium, etc.], alkali metal hydride [e.g. sodium hydride, etc.],
35 alkaline earth metal hydride [e.g. calcium hydride, etc.],

the hydroxide or carbonate or bicarbonate of an alkali metal or an alkaline earth metal [e.g. potassium bicarbonate, etc.] and the like.

This reaction is usually carried out in a solvent such
5 as N,N-dimethylformamide, diethyl ether, tetrahydrofuran, dioxane, benzene, toluene, acetonitrile or any other solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

10

Process 8

The object compound [Ig] of its salt can be prepared by subjecting a compound [If] or its salt to elimination reaction of the N-protective group.

15 Suitable salts of the compounds [If] and [Ig] may be acid addition salts as exemplified for the compound [I].

This reaction is carried out in accordance with a conventional method such as hydrolysis, reduction or the like.

20 The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof,
25 hydrazine, alkylamine [e.g. methylamine, trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo-[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic
30 acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.], an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, hydrogen fluoride, etc.] and an acid addition salt compound [e.g. pyridine hydrochloride,
35 etc.].

The elimination using trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

5 The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, chloroform, tetrachloromethane, dioxane, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or
10 acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

 The reduction method applicable for the elimination reaction may include chemical reduction and catalytic
15 reduction.

 Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic
20 acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

 Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum
25 plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel
30 catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron, etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

35 In case that the N-protective group is benzyl, the

reduction is preferably carried out in the presence of a combination of palladium catalysts [e.g. palladium black, palladium on carbon, etc.] and formic acid or its salt [e.g. ammonium formate, etc.].

- 5 The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in
- 10 liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc. or a mixture thereof.
- 15 The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to heating.

Process 9

- 20 The compound [Ii] or its salt can be prepared by reacting a compound [Ih] or its salt with a compound [XII].
- Suitable salts of the compounds [Ih] and [Ii] may be the same as those exemplified for the compound [I].
- This reaction can be carried out in substantially the
- 25 same manner as Process 7, and therefore the reaction mode and reaction condition [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those explained in Process 7.

30 Process 10

- The compound [Ij] or its salt can be prepared by reacting a compound [II] or its salt with a compound [XIII].
- Suitable salts of the compounds [Ij] and [II] may be the same as those exemplified for the compound [I].
- 35 This reaction can be carried out in substantially the

same manner as Process 7, and therefore the reaction mode and reaction condition [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those explained in Process 7.

- 5 The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

10 It is to be noted that the compound [I] and the other compounds may include one or more stereoisomer(s) such as optical isomer(s) or geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s), and all of such isomers and mixture thereof are included within the scope of this invention.

- 15 Additionally, it is to be noted that any solvate [e.g. enclosure compound (e.g. hydrate, etc.)] of the compound [I] or a pharmaceutically acceptable salt thereof is also included within the scope of this invention.

20 The object compound [I] and pharmaceutically acceptable salts thereof possess strong potentiation of the cholinergic activity, and are useful for the treatment and/or prevention of disorders in the central nervous system for mammals, and more particularly of amnesia, dementia (e.g., senile dementia, Alzheimer's dementia, dementia associated with various
25 diseases such as cerebral vascular dementia, cerebral post-traumatic dementia, dementia due to brain tumor, dementia due to chronic subdural hematoma, dementia due to normal pressure hydrocephalus, post-meningitis dementia, Parkinson's disease type dementia, etc.) and the like. Additionally, the object
30 compound is expected to be useful as therapeutical and/or preventive agents for schizophrenia, depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime
35 sleepiness (narcolepsy), Parkinson's disease or autism.

In order to illustrate the usefulness of the object compound [I], the pharmacological data of the compound [I] is shown in the following.

5 Test

Penile erection in rat

(This test was carried out according to a similar manner to that described in Jpn. J. Pharmacol., Vol. 64, 147-153 (1994))

10

(i) Method

Male Fischer 344 rats at the age of 8 weeks (n=7) were used. All rats were handled 3 minutes a day for three successive days before the tests. The rats were tested in groups of seven and various doses of the test compound were given in semi-randomized order. The test compounds were suspended in 0.5% methyl-cellulose immediately before use, and given intraperitoneally in a volume of 1 ml/kg just before the start of test. Immediately after injection, each rat was placed in a perspex box (25x25x35 cm) and its behavior was observed for 60 minutes, during which time the number of penile erections was counted. A mirror was situated behind each box to facilitate of the rat. Data was expressed as a mean number.

25

(ii) Test Result

Test Compound (Example No.)	Dose (mg/kg)	Penile Erection (number/hr)
2	1	1.14
19	0.32	0.75

30

It is clear that the compound having the above-mentioned

activity ameliorates the memory deficits (i.e. amnesia, dementia, etc.) from the description in the Journal of Pharmacology and Experimental Therapeutics, Vo. 279, No. 3, 1157-1173 (1996). Further, it is expected that the compound
5 having the above-mentioned activity is useful as
therapeutical and/or preventive agent for aforesaid diseases
from some patent applications (e.g. PCT International
Publication No. WO 98/27930, etc.).

For therapeutic purpose, the compound [I] and a
10 pharmaceutically acceptable salt thereof of the present
invention can be used in a form of pharmaceutical preparation
containing one of said compounds, as an active ingredient, in
admixture with a pharmaceutically acceptable carrier such as
an organic or inorganic solid, semi-solid or liquid excipient
15 suitable for oral or parenteral administration. The
pharmaceutical preparations may be capsules, tablets, dragees,
granules, suppositories, solution, suspension, emulsion, or
the like. If desired, there may be included in these
preparations, auxiliary substances, stabilizing agents,
20 wetting or emulsifying agents, buffers and other commonly
used additives.

While the dosage of the compound [I] will vary depending
upon the age and condition of the patient, an average single
dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500
25 mg and 1000 mg of the compound [I] may be effective for
treating the above-mentioned diseases. In general, amounts
between 0.1 mg/body and about 1,000 mg/body may be
administered per day.

30 The following Preparations and Examples are given for
the purpose of illustrating this invention.

Preparation 1

To a solution of 1-benzyl-4-aminopiperidine (50 g) in
35 water (360 ml) was added a solution of di-tert-butyl

dicarbonate (61 g) in acetone (360 ml) dropwise under cooling on an ice-water bath. After stirring for 2.5 hours, a precipitate was collected on a filter, washed with water, and dried. The crude product was poured into a mixture of diisopropyl ether (200 ml) and n-hexane (200 ml) and the mixture was stirred. After filtration, O-tert-butyl N-(1-benzylpiperidin-4-yl)carbamate (66.9 g) was obtained.

NMR (DMSO-d₆, δ): 1.2-1.5 (2H, m), 1.37 (9H, s), 1.66 (2H, br d, J=9.9Hz), 1.91 (2H, br t, J=10.7Hz), 2.73 (2H, distorted d, J=11.8Hz), 3.2 (1H, m), 3.41 (2H, s), 6.75 (1H, d, J=7.8Hz), 7.1-7.4 (5H, m)
MASS (APCI) (m/z): 291

Preparation 2

To a mixture of O-tert-butyl N-(1-benzylpiperidin-4-yl)carbamate (45 g) and 10% palladium on carbon (50% wet, 9 g) in methanol (1 l) was bubbled hydrogen gas under stirring at ambient temperature. The catalyst was removed by glass filter and the solvent was removed under reduced pressure. After rinse with diisopropyl ether, O-tert-butyl N-(piperidin-4-yl)carbamate (28.35 g) was obtained. The washed solvent was removed under reduced pressure, and the residue was rinsed with diisopropyl ether. The second fraction of O-tert-butyl N-(piperidin-4-yl)carbamate (344 mg) was obtained.

NMR (DMSO-d₆, δ): 1.18 (2H, ddd, J=3.8, 11.8, 11.8Hz), 1.37 (9H, s), 1.62 (2H, distorted d, J=10.8Hz), 1.85 (1H, m), 2.38 (2H, dt, J=2.2, 12.0Hz), 2.86 (2H, distorted d, J=12.3Hz), 3.2 (1H, m), 6.72 (1H, br d)
MASS (APCI) (m/z): 201

Preparation 3

To a suspension of O-tert-butyl N-(piperidin-4-yl)carbamate (4.0 g) in dichloromethane (40 ml) were added

pyridine (1.94 ml), dichloromethane (40 ml), acetic anhydride (20.8 ml) and then N,N-dimethylaminopyridine (0.1 g) at ambient temperature. After stirring for 3 hours, the mixture was washed with 0.1N hydrochloric acid, water, and brine.

- 5 After drying with magnesium sulfate, the solvents were removed under reduced pressure. After rinse with diisopropyl ether, O-tert-butyl N-(1-acetylpiperidin-4-yl)carbamate (4.01 g) was obtained.

NMR (DMSO-d₆, δ): 1.23 (2H, m), 1.38 (9H, s), 1.70
10 (2H, distorted t, J=11.4Hz), 1.97 (3H, s), 2.64 (1H, br t, J=11.1Hz), 3.04 (1H, dt, J=2.8, 11.5Hz), 3.42 (1H, m), 3.72 (1H, br d, J=15.0Hz), 4.19 (1H, br d, J=13.1Hz), 6.86 (1H, d, J=7.5Hz)

MASS (APCI) (m/z): 243

15

Preparation 4

- To a solution of O-tert-butyl N-(1-acetylpiperidin-4-yl)carbamate (2.42 g) in dichloromethane (24 ml) was added 4N hydrogen chloride in dioxane (24 ml). The solvents were
20 removed under reduced pressure. After rinse with diisopropyl ether, 1-acetyl-4-aminopiperidine hydrochloride (2.02 g) was obtained.

NMR (DMSO-d₆, δ): 1.41 (2H, m), 1.93 (2H, distorted
t), 2.00 (3H, s), 2.60 (1H, br t, J=10.4Hz), 3.06
25 (1H, br t, J=11.3Hz), 3.12 (1H, m), 3.84 (1H, br d, J=14.0Hz), 4.34 (1H, br d, J=13.0Hz), 8.32 (3H, br s)

MASS (APCI) (m/z): 143

30 Preparation 5

- To a solution of phenyl chloroformate (5.64 g) in dichloromethane (70 ml) was added a solution of 4-aminopyridine (2.84 g) and triethylamine (5.02 ml) in dichloromethane (100 ml) dropwise under cooling on an ice-
35 water bath. After stirring for 1 hour, the solvents were

removed under reduced pressure. A residue was diluted with dichloromethane (200 ml) and water (200 ml). An organic phase was separated and washed with water and brine. After drying with magnesium sulfate, the solvents were removed under reduced pressure. The reaction mixture was diluted with diisopropyl ether and the precipitates were filtered. After rinse with diethyl ether, O-phenyl N-(4-pyridyl)carbamate (5.07 g) was obtained.

NMR (CDCl₃, δ): 7.17 (2H, m), 7.27 (1H, m), 7.3-7.5 (4H, m), 8.50 (2H, dd, J=1.4, 5.0Hz), 8.06 (1H, s)
MASS (APCI) (m/z): 215

Preparation 6

A solution of sulfuryl chloride (3.55 ml) in chloroform (45 ml) was added a solution of 1-acetylpiperazine (5.66 mg) and triethylamine (6.16 ml) in chloroform (15 ml) dropwise under cooling on an ice-water bath. After stirring for 6 hours, a precipitate was collected by filtration. After drying over sodium hydroxide, 1-acetylpiperazine-4-sulfonyl chloride (2.43 g) was obtained.

NMR (CDCl₃, δ): 2.15 (3H, s), 3.35 (4H, m), 3.69 (2H, t, J=5.1Hz), 3.83 (2H, br s)
MASS (APCI) (m/z): 227

Preparation 7

To a solution of 1-benzyl-4-aminopiperidine (1.13 g) in dichloromethane (10 ml) were added a solution of 4-fluorobenzoyl chloride (0.99 g) in dichloromethane (1 ml) and diisopropylethylamine (1.09 ml) under cooling on an ice-water bath. The mixture was warmed to ambient temperature slowly under stirring. The mixture was diluted with dichloromethane and washed with water, saturated aqueous sodium hydrogen carbonate, water, and brine. After drying with magnesium sulfate, the solvents were removed under reduced pressure. A residue was purified by column chromatography (silica gel

100 ml, dichloromethane:methanol = 15:1). After rinse with diisopropyl ether - n-hexane (1:1), N-(1-benzylpiperidin-4-yl)-4-fluorobenzamide (1.31 g) was obtained.

5 NMR (DMSO-d₆, δ): 1.4-1.7 (2H, m), 1.7-1.9 (2H, m),
2.01 (2H, br t, J=10.7Hz), 2.81 (2H, br d,
J=11.6Hz), 3.46 (2H, s), 3.73 (1H, m), 7.2-7.4 (7H,
m), 7.90 (2H, dd, J=5.6, 8.9Hz), 8.26 (1H, br d,
J=7.7Hz)

MASS (APCI) (m/z): 313

10

Preparation 8

The following compound was obtained by using 4-amino-1-benzylpiperidine as a starting compound according to a similar manner to that of Example 2.

15

N-(1-Benzylpiperidin-4-yl)-N'-(4-fluorophenyl)urea

20 NMR (DMSO-d₆, δ): 1.25-1.5 (2H, m), 1.7-1.9 (2H, m),
2.0-2.2 (2H, m), 2.65-2.8 (2H, m), 3.4-3.6 (3H, m),
6.07 (1H, d, J=7.6Hz), 7.05 (2H, t, J=9Hz), 7.2-
7.45 (2H, m), 8.35 (1H, s)

MASS (APCI) (m/z): 328

Preparation 9

25 To a solution of N-(1-benzylpiperidin-4-yl)-N'-(4-fluorophenyl)urea (3.0 g) in a mixture of methanol (15 ml) and tetrahydrofuran (15 ml) was added palladium on carbon (10% w/w, 50% wet, 0.6 g), and the mixture was hydrogenated under atmospheric pressure of hydrogen for 8 hours. The catalyst was filtered off, and the solvents were evaporated
30 under reduced pressure to give a residue, which was triturated with diisopropyl ether to give N-(piperidin-4-yl)-N'-(4-fluorophenyl)urea (1.97 g).

35 NMR (DMSO-d₆, δ): 1.1-1.4 (2H, m), 1.65-1.85 (2H, m),
2.3-2.65 (2H, m), 2.8-3.0 (2H, m), 3.3-3.7 (1H, m),
6.08 (1H, d, J=8Hz), 7.04 (2H, t, J=9Hz), 7.25-7.5

NMR (DMSO- d_6 , δ): 1.1-1.4 (2H, m), 1.65-1.85 (2H, m),
2.3-2.65 (2H, m), 2.8-3.0 (2H, m), 3.3-3.7 (1H, m),
6.08 (1H, d, $J=8\text{Hz}$), 7.04 (2H, t, $J=9\text{Hz}$), 7.25-7.5
(2H, m), 8.33 (1H, s)

5 MASS (APCI) (m/z): 238

Preparation 10

A mixture of N-(1-benzylpiperidin-4-yl)-4-fluorobenzamide (937 mg) and 10% palladium on carbon (50%
10 wet, 0.2 g) in methanol (20 ml) was stirred under hydrogen
atmosphere for 7.5 hours at ambient temperature. The
catalyst was removed by glass filter and the solvent was
removed under reduced pressure. After rinse with
diisopropyl ether, N-(piperidin-4-yl)-4-fluorobenzamide (653
15 mg) was obtained.

NMR (DMSO- d_6 , δ): 1.40 (2H, ddd, $J=4.0, 11.9, 23.8\text{Hz}$),
1.72 (2H, br d, $J=9.5\text{Hz}$), 2.3-2.7 (2H, m), 2.8-3.2
(2H, m), 3.80 (1H, m), 7.27 (2H, t, $J=8.9\text{Hz}$), 7.92
(2H, dd, $J=5.6, 8.9\text{Hz}$), 8.26 (1H, d, $J=7.7\text{Hz}$)

20 MASS (APCI) (m/z): 223

Example 1

To a solution of O-phenyl N-(4-pyridyl)carbamate (446
mg) in 1,2-dichloroethane (5 ml) was added a suspension of
25 1-acetylpiperazine (1.12 g) in 1,2-dichloroethane (20 ml) at
ambient temperature. The mixture was heated at 60°C with
stirring for 9 hours. The mixture was cooled to ambient
temperature, and diluted with dichloromethane and water.
The aqueous phase was separated and adjusted to pH 11.5 with
30 sodium hydroxide solution. Excess sodium chloride was added
to the aqueous solution. The mixture was extracted with a
mixture of dichloromethane and methanol (about 10:1) and the
organic phase was washed with brine. After drying with
magnesium sulfate, the solvents were removed under reduced
35 pressure. A residue was purified by column chromatography

(silica gel 100 ml, dichloromethane:methanol:aqueous ammonia = 10:1:0.1). After rinse with diisopropyl ether, 1-acetyl-4-(4-pyridylaminocarbonyl)piperazine (398 mg) was obtained.

NMR (DMSO-d₆, δ): 2.03 (3H, s), 3.3-3.6 (8H, m), 7.47
5 (2H, dd, J=1.5, 4.8Hz), 8.31 (2H, dd, J=1.5, 4.8Hz), 9.01 (1H, s)

MASS (APCI) (m/z): 271

Example 2

10 To a stirred solution of 1-acetylpiperazine (0.648 g) in tetrahydrofuran (10 ml) was added 4-fluorophenyl isocyanate (0.574 g) at ambient temperature. After stirring at ambient temperature for 1 hour, the solvent was removed by evaporation under reduced pressure, and the residue was
15 triturated with diisopropyl ether to give 1-acetyl-4-(4-fluorophenylcarbamoyl)piperazine (1.25 g).

NMR (DMSO-d₆, δ): 2.03 (3H, s), 3.3-3.6 (8H, m), 7.07
(2H, t, J=9Hz), 7.46 (2H, dd, J=5, 9Hz), 8.61 (1H, s)

20 MASS (APCI) (m/z): 266

Example 3

The following compound was obtained by using 1-tert-butoxycarbonylpiperazine as a starting compound according to
25 a similar manner to that of Example 2.

1-tert-Butoxycarbonyl-4-(4-fluorophenylcarbamoyl)-piperazine

NMR (DMSO-d₆, δ): 1.42 (9H, s), 3.25-3.5 (8H, m), 7.07
30 (2H, t, J=9Hz), 7.45 (2H, dd, J=5, 9Hz), 8.60 (1H, s)

MASS (LD) (m/z): 346.2

Example 4

35 To a solution of pyridine-4-carboxylic acid (1.0 g) and

triethylamine (1.2 ml) in toluene (20 ml) was added
diphenylphosphoryl azide (1.75 ml) at ambient temperature.
The resulting mixture was heated to reflux for 30 minutes
and cooled to 0°C. To the mixture was added 1-tert-
5 butoxycarbonylpiperazine (1.51 g), and the mixture was
allowed to heat to 90°C for 1 hour. After cooling to ambient
temperature, the reaction mixture was taken up into ethyl
acetate, washed in turn with water and brine, dried over
magnesium sulfate, and evaporated under reduced pressure.
10 The residue was chromatographed on silica gel (150 ml)
eluting with 0-7% methanol in dichloromethane. Trituration
with a mixture of diisopropyl ether and ethanol gave 1-tert-
butoxycarbonyl-4-(pyridin-4-ylcarbamoyl)piperazine (0.66 g).
NMR (DMSO-d₆, δ): 1.42 (9H, s), 3.25-3.5 (8H, m), 7.46
15 (2H, d, J=1.5, 5Hz), 8.30 (2H, d, J=1.5, 5Hz),
9.00 (1H, s)
MASS (LD) (m/z): 307.2

Example 5

20 To a suspension of 1-acetyl-4-aminopiperidine
hydrochloride (0.4 g) in dichloromethane (5 ml) were added
in turn pyridine (0.54 ml) and 4-fluorophenyl chloroformate
(0.29 ml) at 0°C. The mixture was allowed to warm to ambient
temperature and stirred for 1 hour, which was taken up into
25 a mixture of water and ethyl acetate. The separated organic
layer was washed in turn with hydrochloric acid (1N),
aqueous sodium hydrogen carbonate, and brine, and dried over
magnesium sulfate. Evaporation under reduced pressure gave
a residue, which was triturated with diisopropyl ether to
30 give 1-acetyl-4-(4-fluorophenoxycarbonylamino)piperidine
(347 mg).
NMR (DMSO-d₆, δ): 1.15-1.55 (2H, m), 1.7-1.95 (2H, m),
2.00 (3H, s), 2.65-2.85 (1H, m), 3.0-3.25 (1H, m),
3.5-3.7 (1H, m), 3.7-3.9 (1H, m), 4.15-4.3 (1H, m),
35 7.05-7.3 (4H, m), 7.86 (1H, d, J=8Hz)

MASS (APCI) (m/z): 281

Example 6

To a suspension of 1-acetyl-4-aminopiperidine
5 hydrochloride (715 mg) in dichloromethane (7 ml) were added
diisopropylethylamine (1.83 ml) and a solution of
4-fluorobenzoyl chloride (0.83 mg) in dichloromethane (2 ml)
at ambient temperature. After stirring for 6.5 hours, the
reaction mixture was diluted with dichloromethane and washed
10 with water, saturated aqueous sodium hydrogen carbonate, and
brine. After drying with magnesium sulfate, the solvents
were removed under reduced pressure. A residue was purified
by column chromatography (silica gel 50 ml,
dichloromethane:methanol = 50:1 to 10:1). After rinse with
15 diisopropyl ether, N-(1-acetylpiperidin-4-yl)-4-
fluorobenzamide (738 mg) was obtained.

NMR (DMSO-d₆, δ): 1.40 (2H, m), 1.81 (2H, distorted t,
J=12.4Hz), 2.01 (3H, s), 2.68 (1H, br t, J=11.4Hz),
3.13 (1H, br t, J=11.6Hz), 3.83 (1H, br t,
20 J=13.9Hz), 4.01 (1H, m), 4.33 (1H, br d, J=13.7Hz),
7.29 (2H, t, J=8.9Hz), 7.92 (2H, dd, J=5.5, 8.8Hz),
8.31 (1H, d, J=7.7Hz)

MASS (APCI) (m/z): 265

25 Example 7

To a suspension of 1-acetyl-4-aminopiperidine
hydrochloride (536 mg) in dichloromethane (5 ml) were added
isonicotinoyl chloride hydrochloride (534 mg) and
diisopropylethylamine (1.05 ml) at ambient temperature.
30 After stirring for 8 hours, the reaction mixture was poured
into water and diluted with dichloromethane. The mixture
was adjusted to pH 8.5 with 1N sodium hydroxide solution.
Sodium chloride was added to the mixture and an organic
phase was separated. The aqueous phase was extracted with
35 dichloromethane and a combined organic phase was dried over

magnesium sulfate. The solvents were removed under reduced pressure. A residue was purified by column chromatography (silica gel 50 ml, dichloromethane:methanol = 10:1). After crystallization from diisopropyl ether:n-hexane,

- 5 N-(1-acetylpiperidin-4-yl)-N-isonicotinamide (477 mg) was obtained.

NMR (DMSO-d₆, δ): 1.4 (2H, m), 1.83 (2H, distorted t, J=11Hz), 2.01 (3H, s), 2.69 (1H, br t, J=11Hz), 3.14 (1H, br t, J=12Hz), 3.83 (1H, br d, J=14.1Hz),
10 4.03 (1H, m), 4.33 (1H, br d, J=13.1Hz), 7.75 (2H, dd, J=1.7, 4.4Hz), 8.62 (1H, d, J=7.5Hz), 8.72 (2H, dd, J=1.6, 4.4Hz)

MASS (APCI) (m/z): 248

15 Example 8

To a suspension of 1-acetyl-4-aminopiperidine hydrochloride (715 mg) in dichloromethane (7 ml) were added diisopropylethylamine (1.83 ml) and a solution of 4-fluorobenzenesulfonyl chloride (0.83 mg) in
20 dichloromethane (2 ml) at ambient temperature. After stirring for 6.5 hours, the reaction mixture was diluted with dichloromethane and washed with water, saturated aqueous sodium hydrogen carbonate, and brine. After drying with magnesium sulfate, the solvents were removed under
25 reduced pressure. A residue was purified by column chromatography (silica gel 50 ml, dichloromethane:methanol = 50:1 to 20:1). After rinse with diisopropyl ether, N-(1-acetylpiperidin-4-yl)-4-fluorobenzenesulfonamide (859 mg) was obtained.

30 NMR (DMSO-d₆, δ): 1.21 (2H, m), 1.54 (2H, m), 1.94 (3H, s), 2.66 (1H, br t, J=10.8Hz), 3.02 (1H, dt, J=2.9, 12.0Hz), 3.22 (1H, m), 3.64 (1H, br d, J=14.0Hz), 4.05 (1H, br d, J=13.2Hz), 7.44 (2H, t, J=8.9Hz), 7.8-8.0 (3H, m)

35 MASS (APCI) (m/z): 301

Example 9

To a solution of O-phenyl N-(4-pyridyl)carbamate (0.81 g) in chloroform (10 ml) were added 1-acetyl-4-aminopiperidine hydrochloride (0.68 g) and triethylamine (1.06 ml) at ambient temperature. After stirring for 1 day, the mixture changed to a solution. The solvents were removed under reduced pressure. A residue was purified by column chromatography (silica gel 100 ml, dichloromethane:methanol = 10:1 to 5:1, and silica gel 50 ml, dichloromethane:methanol:aqueous ammonia = 10:1:0.1). The solvents of desired fractions were removed under reduced pressure. A residue was dissolved with methanol (5 ml) and dichloromethane (5 ml), and 4N hydrogen chloride in dioxane (1.5 ml) was added to the solution. The solvents were removed under reduced pressure, and the residue was evaporated azeotropically with methanol. After crystallization from diisopropyl ether and n-hexane, N-(1-acetylpiperidin-4-yl)-N'-(4-pyridyl)urea (343 mg) was obtained.

20 NMR (DMSO-d₆, δ): 1.1-1.6 (2H, m), 1.77 (2H, m), 2.01 (3H, s), 2.94 (1H, br t, J=10.4Hz), 3.22 (1H, br t, J=10.1Hz), 3.76 (2H, m), 4.05 (1H, d, J=13.6Hz), 7.60 (1H, d, J=7.8Hz), 7.83 (2H, d, J=6.8Hz), 8.52 (2H, d, J=7.1Hz), 11.21 (1H, s), 14.66 (1H, br s)
25 MASS (APCI) (m/z): 263

Example 10

To a suspension of 1-acetyl-4-aminopiperidine hydrochloride (536 mg) in dichloromethane (5 ml) were added 4-fluorophenyl isocyanate (375 μ l) and diisopropylethylamine (575 μ l) at ambient temperature. After stirring for 3 hours, the reaction mixture was diluted with dichloromethane. An organic phase was separated and an aqueous phase was extracted with dichloromethane. A combined organic phase was dried over magnesium sulfate and the solvents were

removed under reduced pressure. After crystallization from diisopropyl ether and n-hexane, N-(1-acetylpiperidin-4-yl)-N'-(4-fluorophenyl)urea (448 mg) was obtained.

5 NMR (DMSO-d₆, δ): 1.1-1.5 (2H, m), 1.80 (2H, distorted t, J=10Hz), 2.00 (3H, s), 2.77 (1H, br d, J=10.8Hz), 3.14 (1H, br d, J=11.1Hz), 3.5-3.9 (2H, m), 4.16 (1H, br d, J=13.2Hz), 6.15 (1H, d, J=7.6Hz), 7.05 (2H, t, J=8.9Hz), 7.40 (2H, dd, J=5.0, 9.2Hz), 8.37 (1H, s)
10 MASS (APCI) (m/z): 280

Example 11

To a solution of 4-(4-fluorobenzoylamino)piperidine (0.25 g) in dichloromethane (5 ml) were added in turn
15 pyridine (0.14 ml) and methyl chloroformate (87 μl) at 0°C. The mixture was allowed to warm to ambient temperature and stirred for 1 hour. To the mixture was added N,N-dimethylaminopyridine (0.13 g) and allowed to stir for another 1 hour. The reaction mixture was taken up into a
20 mixture of water and ethyl acetate. The separated organic layer was washed in turn with hydrochloric acid (1N), aqueous sodium hydrogen carbonate, and brine, and dried over magnesium sulfate. Evaporation under reduced pressure gave a residue, which was triturated with diisopropyl ether to
25 give 4-(4-fluorobenzoylamino)-1-methoxycarbonylpiperidine (0.265 g).

30 NMR (DMSO-d₆, δ): 1.3-1.6 (2H, m), 1.75-1.9 (2H, m), 2.8-3.05 (2H, m), 3.60 (3H, s), 3.85-4.1 (2H, m), 7.29 (2H, t, J=9Hz), 7.90 (2H, dd, J=6, 9Hz), 8.30 (1H, d, J=8Hz)
MASS (APCI) (m/z): 281

Example 12

To a solution of 4-(4-fluorobenzoylamino)piperidine
35 (0.25 g) in pyridine (5 ml) were added in turn

4-trifluorobenzenesulfonyl chloride (0.219 g) and catalytic amount of N,N-dimethylaminopyridine at 0°C.

The mixture was allowed to warm to ambient temperature and stirred for 1 hour, which was taken up into a mixture of
5 water and dichloromethane. The separated organic layer was washed in turn with hydrochloric acid (1N), aqueous sodium hydrogen carbonate, and brine, and dried over magnesium sulfate. Evaporation under reduced pressure gave a residue, which was triturated with diisopropyl ether to give
10 4-(4-fluorobenzoylamino)-1-(4-trifluorophenylsulfonyl)-piperidine (0.38 g).

NMR (DMSO-d₆, δ): 1.45-1.7 (2H, m), 1.8-1.95 (2H, m),
2.35-2.55 (2H, m), 3.5-3.85 (3H, m), 7.28 (2H, t, J=9Hz), 7.50 (2H, t, J=9Hz), 7.75-7.95 (4H, m),
15 8.31 (1H, d, J=8Hz)

MASS (APCI) (m/z): 381

Example 13

To a solution of 4-(4-fluorobenzoylamino)piperidine
20 (0.15 g) in dichloromethane (5 ml) were added in turn pyridine (82 µl) and 4-trifluoromethoxybenzoyl chloride (106 µl) at 0°C. The mixture was allowed to warm to ambient temperature and stirred for 4 hours, which was taken up into a mixture of water and dichloromethane. The separated
25 organic layer was washed in turn with hydrochloric acid (1N), aqueous sodium hydrogen carbonate, and brine, and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure gave 4-(4-fluorobenzoylamino)-1-(4-trifluoromethoxybenzoyl)piperidine (205 mg).

30 NMR (DMSO-d₆, δ): 1.3-1.7 (2H, m), 1.7-2.0 (2H, m),
2.7-3.4 (2H, m), 3.4-3.8 (1H, m), 3.9-4.2 (1H, m),
4.2-4.6 (1H, m), 7.30 (2H, t, J=9Hz), 7.35-7.6 (4H, m), 7.91 (2H, dd, J=6, 9Hz), 8.35 (1H, d, J=8Hz)

MASS (LD) (m/z): 433.2

Example 14

To a solution of 4-(4-fluorobenzoylamino)piperidine (0.15 g) in dichloromethane (5 ml) were added in turn pyridine (0.14 ml) and methanesulfonyl chloride (96 μ l) at 5 0°C. The mixture was allowed to warm to ambient temperature and stirred for 1 hour. To the mixture was added N,N-dimethylaminopyridine (0.13 g) and allowed to stir for another 1 hour. The reaction mixture was taken up into a mixture of water and dichloromethane. The separated organic 10 layer was washed in turn with hydrochloric acid (1N), aqueous sodium hydrogen carbonate, and brine, and dried over magnesium sulfate. Evaporation under reduced pressure gave a residue, which was triturated with diisopropyl ether to give 4-(4-fluorobenzoylamino)-1-methylsulfonylpiperidine 15 (0.30 g).

NMR (DMSO- d_6 , δ): 1.45-1.7 (2H, m), 1.8-2.05 (2H, m), 2.7-2.95 (2H, m), 2.88 (3H, s), 3.5-3.65 (2H, m), 3.8-4.05 (1H, m), 7.30 (2H, t, J=9Hz), 7.91 (2H, dd, J=6, 9Hz), 8.36 (1H, d, J=8Hz)

20 MASS (APCI) (m/z): 301

Example 15

To a solution of N-(piperidin-4-yl)-N'-(4-fluorophenyl)urea (0.3 g) in tetrahydrofuran (4 ml) were 25 added in turn pyridine (0.28 ml), methyl chloroformate (98 μ l) and catalytic amount of N,N-dimethylaminopyridine at 0°C. The mixture was allowed to warm to ambient temperature and stirred for 2 hours. The reaction mixture was taken up into a mixture of water and ethyl acetate. The separated 30 organic layer was washed in turn with hydrochloric acid (1N), aqueous sodium hydrogen carbonate, and brine, and dried over magnesium sulfate. Evaporation under reduced pressure gave a residue, which was triturated with diisopropyl ether to give N-(1-methoxycarbonylpiperidin-4-yl)-N'-(4- 35 fluorophenyl)urea (0.312 g).

NMR. (DMSO-d₆, δ): 1.1-1.4 (2H, m), 1.7-1.9 (2H, m),
2.8-3.1 (2H, m), 3.5-3.75 (1H, m), 3.59 (3H, s),
3.75-3.95 (2H, m), 6.15 (1H, d, J=7.6Hz), 7.05 (2H,
t, J=9Hz), 7.37 (2H, dd, J=5, 9Hz), 8.37 (1H, s)

5 MASS (APCI) (m/z): 296

Example 16

To a solution of N-(piperidin-4-yl)-N'-(4-fluorophenyl)urea (0.3 g) in tetrahydrofuran (4 ml) were
10 added in turn N,N-dimethylaminopyridine (0.23 g) and
4-fluorobenzenesulfonyl chloride (0.25 g) at 0°C. The
mixture was allowed to warm to ambient temperature and
stirred for 1 hour. The reaction mixture was taken up into
a mixture of water and dichloromethane. The separated
15 organic layer was washed in turn with hydrochloric acid (1N),
aqueous sodium hydrogen carbonate, and brine, and dried over
magnesium sulfate. Evaporation under reduced pressure gave
a residue, which was triturated with diisopropyl ether to
give N-(1-(4-fluorophenylsulfonyl)-
20 piperidin-4-yl)-N'-(4-fluorophenyl)urea (0.468 g).

NMR (DMSO-d₆, δ): 1.3-1.6 (2H, m), 1.75-1.95 (2H, m),
2.45-2.7 (2H, m), 3.35-3.6 (3H, m), 6.14 (1H, d,
J=7.5Hz), 7.03 (2H, t, J=9Hz), 7.34 (2H, dd, J=5,
9Hz), 7.50 (2H, t, J=9Hz), 7.75-7.95 (2H, m), 8.31
25 (1H, s)

MASS (APCI) (m/z): 396

Example 17

To a suspension of N-(piperidin-4-yl)-4-fluorobenzamide
30 (0.5 g) in dichloromethane (5 ml) were added pyridine (218
μl), dichloromethane (5 ml) and benzoyl chloride (290 μl) at
ambient temperature. After stirring for 3.5 hours, water (5
ml) was poured into the mixture. An organic layer was
separated, and washed with water and brine. After drying
35 with magnesium sulfate, the solvents were removed under

reduced pressure. A residue was purified by column chromatography (silica gel, toluene:ethyl acetate = 1:1 to ethyl acetate). After rinse with diisopropyl ether, N-(1-benzoylpiperidin-4-yl)-4-fluorobenzamide (515 mg) was
5 obtained.

NMR (DMSO-d₆, δ): 1.50 (2H, br s), 1.85 (2H, br s),
2.8-3.3 (2H, m), 3.61 (1H, m), 4.1 (1H, m), 4.35
(1H, m), 7.29 (2H, t, J=8.9Hz), 7.3-7.5 (5H, m),
7.92 (2H, dd, J=5.6, 8.9Hz), 8.34 (1H, d, J=7.9Hz)

10 MASS (APCI) (m/z): 327

Example 18

To a suspension of N-(piperidin-4-yl)-4-fluorobenzamide (556 mg) in dichloromethane (5 ml) were added pivaloyl
15 chloride (0.37 ml), pyridine (0.24 ml) and
N,N-dimethylaminopyridine (25 mg) at ambient temperature.
After stirring for 1 day, the mixture was diluted with
dichloromethane, and washed with water and brine. After
drying with magnesium sulfate, the solvents were removed
20 under reduced pressure. After trituration with diisopropyl
ether, N-(1-pivaloylpiperidin-4-yl)-4-fluorobenzamide (305
mg) was obtained.

NMR (DMSO-d₆, δ): 1.20 (9H, s), 1.41 (2H, m), 1.7-1.9
(2H, m), 2.91 (2H, br t, J=11.9Hz), 4.07 (1H, m),
25 4.27 (2H, br d, J=13.3Hz), 7.29 (2H, t, J=8.9Hz),
7.92 (2H, dd, J=5.5, 8.9Hz), 8.30 (1H, d, J=7.8Hz)

MASS (APCI) (m/z): 329

Example 19

30 To a suspension of N-(piperidin-4-yl)-4-fluorobenzamide
(556 mg) in dichloromethane (6 ml) were added
cyclopropanecarboxylic acid (0.20 ml), 1-
hydroxybenzotriazole (338 mg) and 1-ethyl-3-(3-
dimethylaminopropyl)carbodiimide hydrochloride (480 mg) at
35 ambient temperature. After stirring for 21 hours, the

mixture was diluted with dichloromethane, and washed with water, saturated aqueous sodium hydrogen carbonate, and brine. After drying with magnesium sulfate, the solvents were removed under reduced pressure. After crystallization from diisopropyl ether, N-(1-cyclopropylcarbonylpiperidin-4-yl)-4-fluorobenzamide (627 mg) was obtained.

NMR (DMSO- d_6 , δ): 0.6-0.8 (4H, m), 1.2-1.6 (2H, m), 1.7-2.0 (2H, m), 1.85 (1H, m), 2.72 (1H, m), 3.21 (1H, m), 4.04 (1H, m), 4.30 (2H, m), 7.29 (2H, t, $J=8.9\text{Hz}$), 7.92 (2H, dd, $J=5.6, 8.9\text{Hz}$), 8.31 (1H, d, $J=7.7\text{Hz}$)

MASS (APCI) (m/z): 313

Example 20

1-tert-Butoxycarbonyl-4-(4-fluorophenylcarbamoyl)-piperazine (0.30 g) was dissolved in a solution of hydrogen chloride in ethyl acetate (4N, 2 ml), and the solution was stirred at ambient temperature for 1 hour. The solvent was removed by evaporation under reduced pressure to give 1-(4-fluorophenylcarbamoyl)piperazine as a white powder, which was taken up into dichloromethane (3 ml), and to the mixture were added in turn pyridine (0.25 ml), 4-trifluoromethoxybenzoyl chloride (0.146 ml), and catalytic amount of N,N-dimethylaminopyridine. After stirring at ambient temperature for 12 hours, the mixture was washed in turn with hydrochloric acid (0.5N), aqueous sodium hydrogen carbonate, and brine, dried over magnesium sulfate, and evaporated under reduced pressure. The residue was chromatographed on silica gel (50 ml) eluting with 0%-3% methanol in dichloromethane to give 1-(4-fluorophenylcarbamoyl)-4-(4-trifluoromethoxybenzoyl)-piperazine (0.19 g).

NMR (DMSO- d_6 , δ): 3.2-3.8 (8H, m), 7.08 (2H, t, $J=9\text{Hz}$), 7.35-7.5 (4H, m), 7.5-7.65 (2H, m)

MASS (LD) (m/z): 434.1

Example 21

The following compound was obtained by using methyl chloroformate as a reactive derivative at the carboxy group according to a similar manner to that of Example 20.

5

1-Methoxycarbonyl-4-(4-fluorophenylcarbamoyl)piperazine

NMR (DMSO-d₆, δ): 3.3-3.5 (8H, m), 3.62 (3H, s), 7.07
(2H, t, J=9Hz), 7.44 (2H, dd, J=5, 9Hz), 8.62 (1H,
s)

10

MASS (APCI) (m/z): 282

Example 22

A mixture of N-acetylpiperidine-4-carboxylic acid (514 mg), 1-hydroxybenzotriazole (405 mg), 1-ethyl-3-(3-
15 dimethylaminopropyl)carbodiimide hydrochloride (575 mg) and
4-fluoroaniline (284.2 ml) in dichloromethane (5 ml) was
stirred for 18 hours at ambient temperature. The mixture
was diluted with dichloromethane and washed with water,
saturated aqueous sodium hydrogen carbonate, water, and
20 brine. After drying with magnesium sulfate, the solvents
were removed under reduced pressure. A residue was purified
by column chromatography (silica gel 40 ml,
dichloromethane:methanol = 15:1). After trituration with
diisopropyl ether, 1-acetyl-4-(4-fluorophenyl)-
25 carbamoylpiperidine (532 mg) was obtained.

NMR (DMSO-d₆, δ): 1.3-1.7 (2H, m), 1.8 (2H, m), 2.01
(3H, s), 2.5 (2H, m), 3.05 (1H, br t, J=10.6Hz),
3.87 (1H, br d, J=14.1Hz), 4.40 (1H, br d,
J=13.1Hz), 7.12 (2H, t, J=8.9Hz), 7.61 (2H, dd,
30 J=5.1, 9.1Hz), 9.96 (1H, s)

MASS (APCI) (m/z): 265

Example 23

A solution of 1-acetylpiperazine-4-sulfonyl chloride
35 (0.91 g) in chloroform (10 ml) were added 4-fluoroaniline

(0.38 ml) and triethylamine (0.56 ml) at ambient temperature.

After stirring for 6 days, the solvents were removed under reduced pressure. A residue was purified by column chromatography (silica gel 100 ml, dichloromethane:methanol = 19:1). After rinse with diisopropyl ether, 1-acetyl-4-(4-fluorophenyl)-sulfamoylpiperazine (716 mg) was obtained.

NMR (CDCl₃, δ): 1.97 (3H, s), 3.09 (4H, m), 3.37 (4H, m), 7.20 (4H, m), 10.00 (1H, s)

10 MASS (APCI) (m/z): 302

Example 24

To a solution of O-tert-butyl (1-acetylpiperidin-4-yl)carbamate (0.97 g) in N,N-dimethylformamide (10 ml) was added 60% sodium hydride (0.18 g) at ambient temperature. After stirring for 40 minutes, 4-fluorobenzyl bromide (0.6 ml) was added to the reaction mixture. After additional stirring for 4 hours, the reaction mixture was poured into a mixture of ethyl acetate (50 ml) and water (10 ml). An organic phase was separated and washed with water and brine. After drying with magnesium sulfate, the solvents were removed under reduced pressure. A residue was purified by column chromatography (silica gel 100 ml, toluene:ethyl acetate = 1:1 to 1:2). After crystallization from diisopropyl ether and n-hexane, O-tert-butyl N-(4-fluorobenzyl)-N-(1-acetylpiperidin-4-yl)carbamate (922 mg) was obtained.

NMR (DMSO-d₆, δ): 1.35 (9H, br s), 1.3-1.8 (4H, m), 1.95 (3H, s), 2.3-2.6 (1H, m), 2.97 (1H, m), 3.80 (1H, br d, J=15.2Hz), 4.0 (1H, m), 4.32 (2H, s), 4.2-4.6 (1H, m), 7.0-7.4 (4H, m).

30 MASS (APCI) (m/z): 295

Example 25

35 To a solution of O-tert-butyl N-(4-fluorobenzyl)-N-(1-

acetylpiperidin-4-yl)carbamate (0.5 g) in dichloromethane (5 ml) was added 4N hydrogen chloride in dioxane (5 ml). The reaction mixture was diluted with diisopropyl ether and the precipitates were collected by filtration. After drying
5 under reduced pressure, 1-acetyl-4-(4-fluorobenzyl)-aminopiperidine hydrochloride (409 mg) was obtained.

NMR (DMSO- d_6 +D₂O, δ): 1.54 (2H, m), 2.02 (3H, s),
2.0-2.3 (2H, m), 2.4-2.7 (1H, m), 3.04 (1H, br t, J=12.1Hz), 3.29 (1H, m), 3.9 (1H, m), 4.17 (2H, s),
10 4.44 (1H, br d, J=13.6Hz), 7.27 (2H, t, J=8.9Hz),
7.66 (2H, br t, J=6.8Hz)

MASS (APCI) (m/z): 251

Example 26

15 To a solution of N-(1-acetylpiperidin-4-yl)-4-fluorobenzamide (529 mg) in N,N-dimethylformamide (5 ml) was added sodium hydride (0.1 g). After stirring for 45 minutes, methyl iodide (623 ml) was added to the solution. After stirring for 45 minutes, the mixture was diluted with ethyl
20 acetate (100 ml) and water (50 ml). An organic phase was separated, and washed with water and brine. After drying with magnesium sulfate, the solvents were removed under reduced pressure. After trituration with diisopropyl ether, N-(1-acetylpiperidin-4-yl)-N-methyl-4-fluorobenzamide (248
25 mg) was obtained.

NMR (DMSO- d_6 , δ): 1.65 (4H, m), 2.00 (3H, s), 2.78
(3H, s), 3.8 (1H, m), 4.4 (1H, m), 2.0-4.6 (3H, br m), 7.26 (2H, t, J=8.9Hz), 7.46 (2H, dd, J=5.6, 8.7Hz)

30 MASS (APCI) (m/z): 301

Example 27

A suspension of 1-acetylpiperazine (0.627 g), 2-chloro-4'-fluoroacetophenone (0.844 g), and potassium hydrogen
35 carbonate (0.735 g) in acetonitrile (12 ml) was stirred at

ambient temperature for 3 days. After removal of the solid by filtration, the filtrate was evaporated under reduced pressure to give a residue, which was chromatographed on silica gel (100 ml) eluting with 0%-5% methanol in dichloromethane. The objective compound of the free form was taken up into ethyl acetate (2 ml) and to the solution was added a solution of hydrogen chloride in ethyl acetate (4N, 2 ml). The resulting precipitate was collected by filtration, washed with diisopropyl ether, and dried in vacuo to give 1-acetyl-4-(4-fluorophenylcarbonylmethyl)-piperazine hydrochloride (1.47 g).

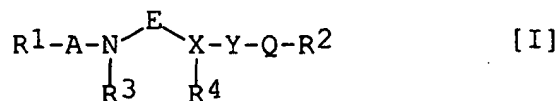
NMR (DMSO- d_6 , δ): 2.06 (3H, s), 2.95-3.8 (6H, m), 3.9-4.15 (1H, m), 4.2-4.45 (1H, m), 5.13 (2H, s), 7.48 (2H, t, $J=9$ Hz), 8.09 (2H, dd, $J=5, 9$ Hz)

MASS (APCI) (m/z): 265

C L A I M S

1. A compound of the formula:

5



wherein R^1 is acyl,

10

R^2 is lower alkyl, lower alkoxy, lower
alkylamino, lower alkenyl, lower
alkenyloxy, lower alkenylamino, lower
alkynyl, lower alkynyloxy, lower
alkynylamino, cyclo(lower)alkyl,
15 cyclo(lower)alkyloxy,
cyclo(lower)alkylamino, aryl, aryloxy,
arylamino, a heterocyclic group or amino
substituted with a heterocyclic group,
each of which may be substituted with
20 suitable substituent(s); or acyl;

A is a single bond, $\text{-}\overset{\text{O}}{\parallel}\text{C-}$ or $\text{-SO}_2\text{-}$,

E is lower alkylene optionally substituted with
suitable substituent(s),

25

X is CH or N,

Y is a single bond, lower alkylene or $\text{-}\overset{\text{R}^5}{\underset{|}{\text{N}}}\text{-}$
(wherein R^5 is hydrogen, lower alkyl,
substituted-lower alkyl, an N-protective
group, aryl, acyl or a heterocyclic group),

30

Q is $\text{-CH}_2\text{-}$, $\text{-}\overset{\text{O}}{\parallel}\text{C-}$, $\text{-SO}_2\text{-}$ or -N=CH- , and

R^3 and R^4 are each hydrogen or lower alkyl, or
are taken together to form lower alkylene
optionally condensed with a cyclic
35 hydrocarbon or a heterocyclic ring,

provided that when X is N,

then 1) Y is a single bond, and

Q is $-\text{CH}_2-$, $-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-$ or $-\text{SO}_2-$, or

5

2) Y is lower alkylene,

and pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein

10 R^2 is aryl, aryloxy or arylamino, each aryl of which
may be substituted with halogen; pyridyl; or
pyridylamino;

A is a single bond,

E is ethylene,

X is CH or N,

15

Y is a single bond, lower alkylene or $-\overset{\text{R}^5}{\underset{|}{\text{N}}}-$

(wherein R^5 is hydrogen, lower alkyl or
an N-protective group),

Q is $-\text{CH}_2-$, $-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-$ or $-\text{SO}_2-$, and

20

R^3 and R^4 are taken together to form ethylene.

3. A compound according to claim 2, wherein

R^1 is lower alkanoyl, esterified carboxy, substituted
or unsubstituted aroyl, lower alkylsulfonyl,
25 substituted or unsubstituted arylsulfonyl, or
cyclo(lower)alkylcarbonyl, and

R^2 is aryl or arylamino, each aryl of which may be
substituted with halogen.

30 4. A compound according to claim 3, wherein

R^1 is lower alkanoyl, lower alkoxycarbonyl, aroyl,
aroyl substituted with halo(lower)alkoxy, lower
alkylsulfonyl, arylsulfonyl, arylsulfonyl
substituted with halogen, or
35 cyclo(lower)alkylcarbonyl,

X is CH,
 Y is a single bond or $\begin{array}{c} \text{H} \\ | \\ -\text{N}- \end{array}$, and

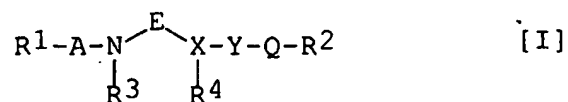
5 Q is $\begin{array}{c} \text{O} \\ || \\ -\text{C}- \end{array}$ or $-\text{SO}_2-$.

5. A compound according to claim 3, wherein
 R^1 is lower alkanoyl, lower alkoxy carbonyl, aroyl,
 10 aroyl substituted with halo(lower)alkoxy, lower
 alkylsulfonyl, arylsulfonyl, arylsulfonyl
 substituted with halogen, or
 cyclo(lower)alkylcarbonyl,
 X is N,
 Y is a single bond or lower alkylene, and
 15 Q is $\begin{array}{c} \text{O} \\ || \\ -\text{C}- \end{array}$ or $-\text{SO}_2-$.

6. A compound according to claim 4, wherein
 20 Y is $\begin{array}{c} \text{H} \\ | \\ -\text{N}- \end{array}$, and
 Q is $\begin{array}{c} \text{O} \\ || \\ -\text{C}- \end{array}$.

7. A compound according to claim 5, wherein
 25 Y is a single bond, and
 Q is $\begin{array}{c} \text{O} \\ || \\ -\text{C}- \end{array}$.

8. A process for preparing a compound of the formula:
 30



wherein R^1 is acyl,

5 R^2 is lower alkyl, lower alkoxy, lower
 alkylamino, lower alkenyl, lower
 alkenyloxy, lower alkenylamino, lower
 alkynyl, lower alkynyloxy, lower
 alkynylamino, cyclo(lower)alkyl,
 cyclo(lower)alkyloxy,
 cyclo(lower)alkylamino, aryl, aryloxy,
 arylamino, a heterocyclic group or amino
 10 substituted with a heterocyclic group,
 each of which may be substituted with
 suitable substituent(s); or acyl;

15 A is a single bond, $\overset{\text{O}}{\parallel}\text{C}-$ or $-\text{SO}_2-$,
 E is lower alkylene optionally substituted with
 suitable substituent(s),

X is CH or N,
 Y is a single bond, lower alkylene or $-\overset{\text{R}^5}{\text{N}}-$
 (wherein R^5 is hydrogen, lower alkyl,
 20 substituted-lower alkyl, an N-protective
 group, aryl, acyl or a heterocyclic group),

Q is $-\text{CH}_2-$, $\overset{\text{O}}{\parallel}\text{C}-$, $-\text{SO}_2-$ or $-\text{N}=\text{CH}-$, and
 25 R^3 and R^4 are each hydrogen or lower alkyl, or
 are taken together to form lower alkylene
 optionally condensed with a cyclic
 hydrocarbon or a heterocyclic ring,

provided that when X is N,

then 1) Y is a single bond, and

30 Q is $-\text{CH}_2-$, $\overset{\text{O}}{\parallel}\text{C}-$ or $-\text{SO}_2-$, or
 2) Y is lower alkylene,

or pharmaceutically acceptable salt thereof,
 which comprises,

35 1) reacting a compound of the formula:

5



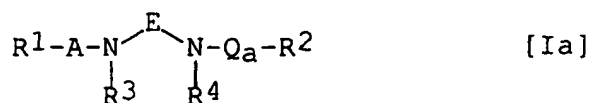
or its salt with a compound of the formula:

10



or its reactive derivative at the carboxy or sulfo group, or a salt thereof to provide a compound of the formula:

15



or its salt, in the above formulas,
 R^1 , R^2 , R^3 , R^4 , A and E are each as defined above, and
 Q_a is $\text{-}\overset{\text{O}}{\parallel}\text{C-}$ or $\text{-SO}_2\text{-}$, or

20

2) reacting a compound of the formula:

25

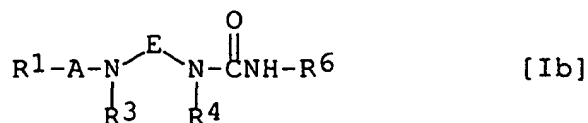


or its salt with a compound of the formula:

30



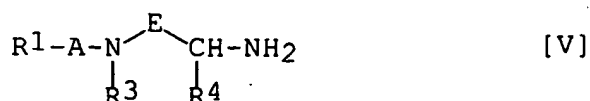
to provide a compound of the formula:



or its salt, in the above formulas,
 R^1 , R^3 , R^4 , A and E are each as defined above, and
 5 R^6 is aryl which may be substituted with suitable
 substituent(s); or pyridyl, or

3) reacting a compound of the formula:

10

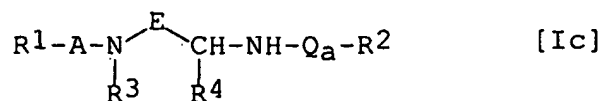


or its salt with a compound of the formula:

15



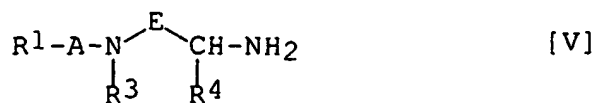
or its reactive derivative at the carboxy or sulfo
 group, or a salt thereof to provide a compound of the
 20 formula:



25

or its salt, in the above formulas,
 R^1 , R^2 , R^3 , R^4 , A, E and Q_a are each as defined above,
 or

30 4) reacting a compound of the formula:

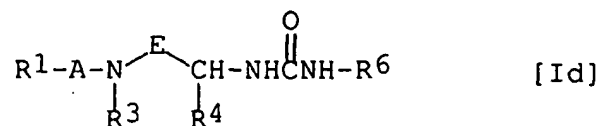


35

or its salt with a compound of the formula:

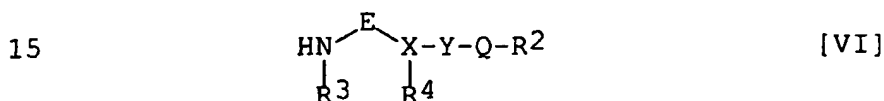


5 to provide a compound of the formula:

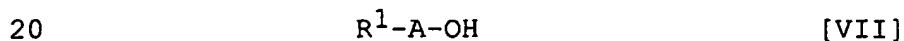


10 or its salt, in the above formulas,
 R^1 , R^3 , R^4 , R^6 , A and E are each as defined above, or

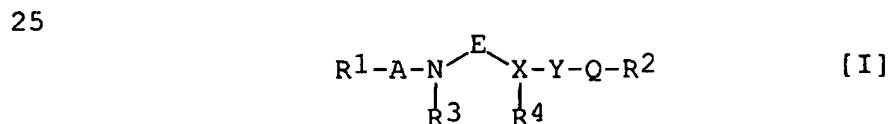
5) reacting a compound of the formula:



or its salt with a compound of the formula:

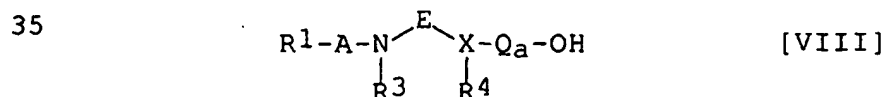


or its reactive derivative at the carboxy or sulfo group, or a salt thereof to provide a compound of the formula:



or its salt, in the above formulas,
 R^1 , R^2 , R^3 , R^4 , A, E, X, Y and Q are each as defined
 30 above, or

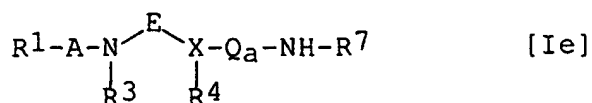
6) reacting a compound of the formula:



or its reactive derivative at the carboxy or sulfo
group, or a salt thereof with a compound of the
formula:



or its salt to provide a compound of the formula:



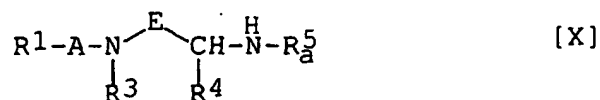
or its salt, in the above formulas,

R^1 , R^3 , R^4 , A, E, X and Q_a are each as defined above,

and

R^7 is lower alkyl, lower alkenyl, lower alkynyl,
cyclo(lower)alkyl, aryl or a heterocyclic group,
each of which may be substituted with suitable
substituent(s), or

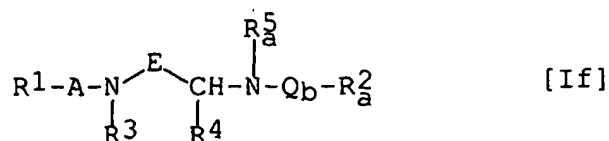
7) reacting a compound of the formula:



or its salt with a compound of the formula:



to provide a compound of the formula:



or its salt, in the above formulas,

R^1 , R^3 , R^4 , A and E are each as defined above,

R_a^5 is an N-protective group,

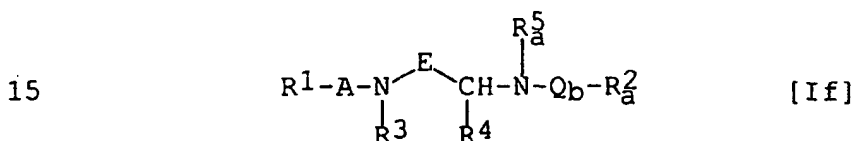
R_a^2 is lower alkyl, lower alkenyl, lower alkynyl,

5 cyclo(lower)alkyl, aryl or a heterocyclic group,
each of which may be substituted with suitable
substituent(s),

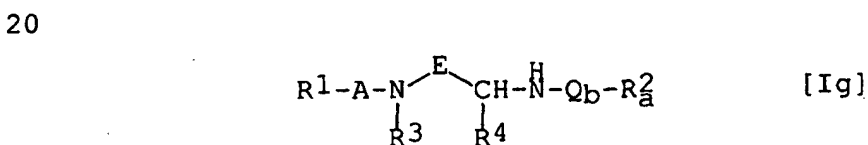
Q_b is $-\text{CH}_2-$, $-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-$, $-\text{SO}_2-$, and

10 Z_a is an acid residue, or

8) subjecting a compound of the formula:



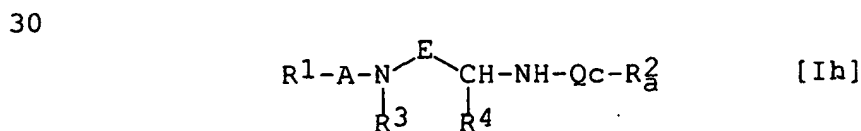
or its salt to elimination reaction of the N-protective
group to provide a compound of the formula:



or its salt, in the above formulas,

25 R^1 , R_a^2 , R^3 , R^4 , A, E and Q_b , are each as defined above,
or

9) reacting a compound of the formula:

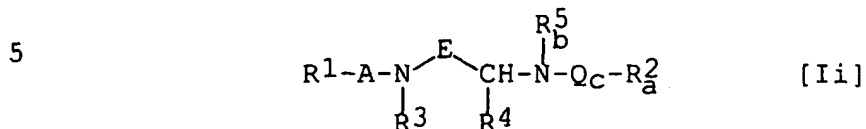


or its salt with a compound of the formula:

35



to provide a compound of the formula:



or its salt, in the above formulas,

R^1 , R_a^2 , R^3 , R^4 , A and E are each as defined above,

Z_b is an acid residue,

Q_c is $\begin{array}{c} O \\ || \\ -C- \end{array}$, and

R_b^5 is lower alkyl, or

10) reacting a compound of the formula:



or its salt with a compound of the formula:



to provide a compound of the formula:



or its salt, in the above formulas,

R^1 , R^2 , R^3 , R^4 , A, E and Q_a are each as defined above,

Z_c is an acid residue, and

Y_a is lower alkylene.

9. A pharmaceutical composition comprising a compound of claim 1, as an active ingredient, in association with a

pharmaceutically acceptable, substantially non-toxic carrier or excipient.

10. A compound of claim 1 for use as a medicament.

5

11. A method for therapeutic treatment and/or prevention of amnesia or dementia which comprises administering an effective amount of a compound of claim 1 to mammals.

10 12. Use of a compound of claim 1 for manufacture of a medicament for treating and/or preventing amnesia or dementia in mammals.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 00/00017

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D211/58 C07D213/75 C07D211/96 C07D295/20 C07D295/18
C07D295/22 A61K31/445 A61K31/496 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 308 337 A (MITSUBISHI KASEI CORP.) 22 March 1989 (1989-03-22) page 4, line 15; claims	1-4, 9-12
X	EP 0 299 493 A (SHIONOGI & CO., LTD.) 18 January 1989 (1989-01-18) claims 1,5-10	1-3, 5, 9-12
X	WO 97 28141 A (PIERRE FABRE MEDICAMENT) 7 August 1997 (1997-08-07) examples 2, 5,10, 11, 14, 26, 27, 28 claims 1,5,7-915-17	1-3, 5, 9-12
X	WO 97 17957 A (SMITHKLINE BEECHAM CORP.) 22 May 1997 (1997-05-22) page 6, compound 3 claims 1,5	1-4, 6, 9, 10
	--- -/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

7 April 2000

Date of mailing of the international search report

14/04/2000

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Authorized officer

Hass, C

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 00/00017

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 22 40 665 A (CHEMISCHE WERKE ALBERT AG) 7 March 1974 (1974-03-07) table 1, compounds 45-52 and 55-59 page 5, line 20 - line 25	1-3,5,9, 10
X	EP 0 002 401 A (SYNTHELABO) 13 June 1979 (1979-06-13) page 1, formula (I); page 15, compounds no. 15-19 claims 1,6	1-3,5,9, 10
X	WO 96 31501 A (SCHERING CORP.) 10 October 1996 (1996-10-10) page 71 -page 77; claims 1,6; examples 1-7,12	1-3,5,9, 10
X	DE 25 45 501 A (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD.) 22 April 1976 (1976-04-22) page 9, formula; page 15, compound no. 102 claims 1,20	1-4,9,10
X	DE 23 11 570 A (JOHN WYETH & BROTHER LTD.) 13 September 1973 (1973-09-13) claims 1,5-7,9,14,27	1-4,9,10
X	EP 0 625 507 A (NISSHIN FLOUR MILLING CO., LTD.) 23 November 1994 (1994-11-23) claims 1,7,9; examples 94,128,129,131,133	1-7,9,10
X	WO 97 11069 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 27 March 1997 (1997-03-27) claims 1,8,9	1-3,5,9, 10
X	EP 0 255 134 A (OTSUKA PHARMACEUTICAL CO., LTD.) 3 February 1988 (1988-02-03) table 1, reference examples no. 2-4; table 3, examples no. 20-22; table 6, examples no. 44, 45, 48, 49, 83, 84	1-6
X	CA 2 077 252 A (ACIC (CANADA) INC.) 1 March 1994 (1994-03-01) claims 9-12	1-3,5
X	EP 0 628 310 A (BAYER AG) 14 December 1994 (1994-12-14) page 6, line 40; example 1; table 1	1-4,6
X	US 3 647 805 A (T. IRIKURA ET AL.) 7 March 1972 (1972-03-07) claims 8,9,16	1-4,6
X	DE 19 38 512 A (KYORIN SEIYAKU K.K.) 14 January 1971 (1971-01-14) examples 12,24	1-4,6
	-/-	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 00/00017

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 700 913 A (HOECHST-ROUSSEL PHARMACEUTICALS INC.) 13 June 1996 (1996-06-13) claim 10 ---	1-4
X	WO 94 22826 A (OTSUKA PHARMACEUTICAL CO., LTD.) 13 October 1994 (1994-10-13) claims 1,2,33-41 ---	1-3
X	US 5 723 490 A (R. D. TUNG) 3 March 1998 (1998-03-03) columns 25 and 26, compounds 227 and 229 ---	1
Y	WO 98 27930 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 2 July 1998 (1998-07-02) cited in the application claims ---	1-3,5, 9-12
Y	WO 98 35951 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 20 August 1998 (1998-08-20) cited in the application claims ---	1-3,5, 8-12
Y	EP 0 436 734 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 17 July 1991 (1991-07-17) claims & WO 91 01979 A cited in the application ---	1-3,5, 8-12
Y	WO 98 25914 A (FUJISAWA PHARMACEUTICAL CO., LTD.) 18 June 1998 (1998-06-18) claims 1,4-7 ---	1-3,5, 9-12
A	US 5 346 907 A (J. F. KERWIN ET AL.) 13 September 1994 (1994-09-13) claims 1,4-6; examples 61,62,94-116 -----	1,9-12

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 00/00017

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 11
is directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 00/00017

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 308337 A	22-03-1989	JP 1075484 A	22-03-1989
		JP 1966859 C	18-09-1995
		JP 6096575 B	30-11-1994
		AT 77389 T	15-07-1992
		CA 1320310 A	13-07-1993
		DE 3872127 A	23-07-1992
		HU 47928 A	28-04-1989
		KR 9711296 B	09-07-1997
		US 4880819 A	14-11-1989
EP 299493 A	18-01-1989	AT 106868 T	15-06-1994
		AU 608025 B	21-03-1991
		CA 1322199 A	14-09-1993
		DE 3889987 D	14-07-1994
		DE 3889987 T	15-09-1994
		DK 393488 A	16-01-1989
		ES 2056860 T	16-10-1994
		JP 1104041 A	21-04-1989
		JP 2552905 B	13-11-1996
		KR 9006742 B	20-09-1990
		US 4904663 A	27-02-1990
WO 9728141 A	07-08-1997	FR 2744449 A	08-08-1997
		AU 1607497 A	22-08-1997
		BR 9707251 A	06-04-1999
		CN 1214047 A	14-04-1999
		EP 0880512 A	02-12-1998
WO 9717957 A	22-05-1997	EP 0873117 A	28-10-1998
		JP 2000500465 T	18-01-2000
DE 2240665 A	07-03-1974	DE 2157424 A	24-05-1973
		AT 336625 B	10-05-1977
		AT 469674 A	15-09-1976
		AT 327207 B	26-01-1976
		AT 469774 A	15-04-1975
		AT 336626 B	10-05-1977
		AT 327203 B	26-01-1976
		AT 981272 A	15-04-1975
		BE 791501 A	17-05-1973
		CA 1025866 A	07-02-1978
		CH 613202 A	14-09-1979
		CH 612430 A	31-07-1979
		CH 592080 A	14-10-1977
		CH 590265 A	29-07-1977
		ES 408565 A	01-11-1975
		FR 2160611 A	29-06-1973
		GB 1407854 A	24-09-1975
		JP 1004705 C	30-06-1980
		JP 52053871 A	30-04-1977
		JP 54040555 B	04-12-1979
		JP 52053872 A	30-04-1977
		JP 55019219 B	24-05-1980
		JP 52053873 A	30-04-1977
		JP 57060350 B	18-12-1982
		JP 1032329 C	29-01-1981
		JP 48061484 A	28-08-1973
		JP 55023831 B	25-06-1980

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 00/00017

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2240665 A		NL 7215416 A,B, SE 408423 B US 4374990 A US 4115569 A AT 923274 A	22-05-1973 11-06-1979 22-02-1983 19-09-1978 15-09-1976
EP 2401 A	13-06-1979	FR 2409994 A FR 2439195 A AR 225604 A AT 366679 B AT 840578 A AU 517219 B AU 4188478 A CA 1101858 A DK 519678 A ES 475299 A FI 783586 A GR 65321 A IE 47677 B IL 56021 A IT 1101422 B JP 1317177 C JP 54081280 A JP 60039273 B MX 5009 E NO 783933 A NZ 188982 A PT 68821 A US 4243665 A ZA 7806553 A	22-06-1979 16-05-1980 15-04-1982 26-04-1982 15-09-1981 16-07-1981 31-05-1979 26-05-1981 25-05-1979 16-04-1979 25-05-1979 11-08-1980 16-05-1984 13-09-1981 28-09-1985 15-05-1986 28-06-1979 05-09-1985 14-02-1983 28-05-1979 05-03-1980 01-12-1978 06-01-1981 31-10-1979
WO 9631501 A	10-10-1996	AU 5432696 A CA 2217351 A EP 0820452 A JP 10511979 T ZA 9602694 A	23-10-1996 10-10-1996 28-01-1998 17-11-1998 03-10-1996
DE 2545501 A	22-04-1976	JP 51052176 A AU 8564375 A BE 834247 A FR 2287228 A NL 7511857 A SE 7511408 A	08-05-1976 21-04-1977 02-02-1976 07-05-1976 14-04-1976 13-04-1976
DE 2311570 A	13-09-1973	GB 1416872 A AU 467944 B AU 5242173 A BE 855713 A CH 576964 A CH 577476 A FR 2181807 A HK 10279 A JP 1283088 C JP 49000273 A JP 60004187 B KE 2916 A US 3971787 A US 3971789 A	10-12-1975 18-12-1975 17-10-1974 03-10-1977 30-06-1976 15-07-1976 07-12-1973 09-03-1979 27-09-1985 05-01-1974 01-02-1985 30-03-1979 27-07-1976 27-07-1976

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 00/00017

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2311570 A		IN 138602 A	28-02-1976
EP 625507 A	23-11-1994	CA 2123728 A	22-11-1994
		DE 69404382 D	04-09-1997
		DE 69404382 T	05-03-1998
		JP 7258200 A	09-10-1995
		US 5621010 A	15-04-1997
WO 9711069 A	27-03-1997	AU 6999796 A	09-04-1997
		EP 0861243 A	02-09-1998
		US 6008229 A	28-12-1999
EP 255134 A	03-02-1988	JP 2025271 C	26-02-1996
		JP 7045493 B	17-05-1995
		JP 64003182 A	06-01-1989
		JP 1964561 C	25-08-1995
		JP 6096555 B	30-11-1994
		JP 63035562 A	16-02-1988
		DE 3784401 A	08-04-1993
		DK 397387 A	01-02-1988
		ES 2053480 T	01-08-1994
		US 4886809 A	12-12-1989
		US 5071856 A	10-12-1991
		US 5306719 A	26-04-1994
CA 2077252 A	01-03-1994	AU 4938593 A	29-03-1994
		WO 9405628 A	17-03-1994
		EP 0656885 A	14-06-1995
		US 5686612 A	11-11-1997
		US 5675006 A	07-10-1997
EP 628310 A	14-12-1994	DE 4319038 A	15-12-1994
		JP 7330761 A	19-12-1995
		US 5492918 A	20-02-1996
US 3647805 A	07-03-1972	NONE	
DE 1938512 A	14-01-1971	JP 49039679 B	28-10-1974
		BE 736840 A	31-12-1969
		CA 931574 A	07-08-1973
		CA 958717 A	03-12-1974
		CA 948203 A	28-05-1974
		DE 1967324 C	22-04-1982
		ES 369746 A	01-04-1971
		ES 378466 A	16-06-1972
		ES 378467 A	16-06-1972
		FR 2048024 A	19-03-1971
		GB 1276812 A	07-06-1972
		GB 1276813 A	07-06-1972
EP 700913 A	13-03-1996	US 5500423 A	19-03-1996
		AT 166876 T	15-06-1998
		CA 2157860 A	10-03-1996
		DE 69502783 D	09-07-1998
		DE 69502783 T	12-11-1998
		ES 2118483 T	16-09-1998
		JP 8092251 A	09-04-1996
		US 5563272 A	08-10-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 00/00017

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9422826 A	13-10-1994	AU 674207 B	12-12-1996
		AU 6292894 A	24-10-1994
		CA 2136999 A	13-10-1994
		CN 1104412 A	28-06-1995
		EP 0650476 A	03-05-1995
		JP 2825755 B	18-11-1998
		JP 6340627 A	13-12-1994
		US 5656642 A	12-08-1997
		US 5760058 A	02-06-1998
US 5723490 A	03-03-1998	US 5783701 A	21-07-1998
		US 5585397 A	17-12-1996
		AU 706732 B	24-06-1999
		AU 5559696 A	07-11-1996
		BG 102048 A	31-08-1998
		BR 9608032 A	12-01-1999
		CA 2217737 A	24-10-1996
		CN 1181755 A	13-05-1998
		CZ 9703293 A	18-03-1998
		EP 0846110 A	10-06-1998
		HU 9801877 A	28-09-1999
		JP 10509739 T	22-09-1998
		NO 974722 A	13-10-1997
		PL 322877 A	02-03-1998
		SK 143197 A	08-04-1998
		WO 9633184 A	24-10-1996
		US 5977137 A	02-11-1999
		US 5856353 A	05-01-1999
		AP 390 A	02-08-1995
		AT 178598 T	15-04-1999
		AU 691160 B	14-05-1998
		AU 4852093 A	29-03-1994
		BG 62488 B	30-12-1999
		BG 99540 A	30-11-1995
		BR 1100824 A	31-08-1999
		CA 2143208 A	17-03-1994
		CN 1087347 A	01-06-1994
		CZ 9500587 A	13-12-1995
		DE 69324369 D	12-05-1999
		DE 69324369 T	26-08-1999
		EP 0659181 A	28-06-1995
		EP 0885887 A	23-12-1998
		ES 2131589 T	01-08-1999
		FI 951059 A	18-04-1995
		GR 3030719 T	30-11-1999
		HU 71892 A	28-02-1996
		JP 8501299 T	13-02-1996
		LT 917 A, B	25-11-1994
		NO 950876 A	08-05-1995
		NZ 256238 A	24-04-1997
		NZ 314376 A	28-10-1998
		PL 307858 A	26-06-1995
		SG 43862 A	14-11-1997
		SK 29395 A	13-09-1995
		WO 9405639 A	17-03-1994
WO 9827930 A	02-07-1998	EP 0942726 A	22-09-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 00/00017

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9835951	A	20-08-1998	EP	0968201 A	05-01-2000
EP 436734	A	17-07-1991	DE	69022965 D	16-11-1995
			DE	69022965 T	04-04-1996
			DK	436734 T	20-11-1995
			HK	64196 A	19-04-1996
			WO	9101979 A	21-02-1991
			JP	2531304 B	04-09-1996
			US	5250528 A	05-10-1993
WO 9825914	A	18-06-1998	AU	5136898 A	03-07-1998
			EP	0944612 A	29-09-1999
US 5346907	A	13-09-1994	EP	0336356 A	11-10-1989
			EP	0442878 A	28-08-1991
			JP	3503650 T	15-08-1991
			WO	8910355 A	02-11-1989
			CA	2062755 A	08-01-1991
			EP	0480969 A	22-04-1992
			GR	90100516 A,B	10-12-1991
			JP	4506660 T	19-11-1992
			PT	94623 A	20-03-1991
			WO	9100725 A	24-01-1991